ANNALS OF THE RHEUMATIC DISEASES

PSYCHOLOGICAL FACTORS AND PAIN IN THE ASSESSMENT OF RHEUMATOID THERAPY*

BY

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During the past year, with the advent of potent therapy by means of cortisone and ACTH, a large series of substances have been tried in rheumatoid arthritis, and several authors have shown that methods are now being evolved whereby the value of any particular therapy can be decisively assessed. Discrepancies between the results of therapeutic trials in different series have shown the necessity of careful control in such trials to eliminate psychological factors.

In many diseases psychological factors frequently produce changes in the nature or severity of symptoms as well as in the emotional attitude of the patient. These changes in symptoms may not be accompanied by any changes in the actual disease process, though psychological factors frequently directly influence the disease process, as in peptic ulceration. These interpolating factors can complicate the assessment of therapy, particularly in disease where objective data may not be readily available. Such considerations apply to rheumatoid arthritis because here the clinical picture is so often dominated by pain, the chief *modus operandi* of psychological factors in this disease. This situation helps to account for the vast number of so-called remedies which have been so readily accepted in the past by doctor and patient alike.

The relationship between psychological factors and pain in general is a close one, and has been the subject of intensive study and experimental analysis by Wolff and Goodell (1943), who showed that the cutaneous pain threshold could be altered considerably, even in critical subjects, by psychological influences.

In a series of experiments Wolf (1950) demonstrated the influence of psychological reactions on the autonomic responses to drugs acting on the gastric mucosa of a patient with a gastric fistula. It would be of interest to investigate in rheumatoid arthritis the effect of psychological factors and pain on autonomic responses, such as the circulatory changes described by Janus (1950).

Placebo Effects in a Series of Uncontrolled Cases

The effect of psychological factors in the course of rheumatoid therapy was well seen in a series of patients treated with DOCA and ascorbic acid. Eighteen unselected patients with rheumatoid arthritis were given injections of 2·5 mg.

* Read before the Heberden Society, December 9, 1950.

deoxycortone by intramuscular injection and 500 mg. ascorbic acid by the intravenous route. The patients were told that they were being given a new type of treatment which had given very good results elsewhere. They were asked to watch for, and carefully observe, any effect on joint symptoms, appetite, and well-being. This, together with the current publicity of the remarkable effects of cortisone therapy, which many of them had read about, engendered in most, though not all, of the patients an attitude of hopeful anticipation, which was reflected in the results that followed. Observations were made on the amount of spontaneous pain, joint movement, and ability to carry out certain actions such as walking, sitting, and standing. The power of grip was measured with a calibrated spring grip-meter, and joint tenderness was graded by the response to firm pressure on the joints. By these criteria, twelve showed improvement after the initial injection, and in six there was no appreciable change. Objective observations such as joint swelling, sedimentation rate, and pyrexia were not significantly altered. In the light of a controlled investigation which was then carried out, and which was entirely negative in its results, it was concluded that in the preliminary uncontrolled trial, the changes observed were essentially placebo effects; i.e. effects produced not directly by the agents administered, but by accompanying psychological responses.

Cases Illustrating Marked Placebo Effects.—In the twelve patients who showed subjective improvement, the response was remarkable in several cases.

(1) *Male, aged 51,* with active disease of four years' duration, lost all his pain, joint tenderness, and stiffness. Whereas before the injection he could only walk slowly and painfully, after it he spontaneously leapt over beds and ran down the ward. Power of grip was increased, and he became very euphoric and anxious to demonstrate his improvement. He had been told to watch the effect on his appetite, and this was rapidly and markedly increased. If a film had been made of this patient the result would have been more spectacular than that seen in the film on the effect of cortisone therapy, shown by Dr. Hench to the Heberden Society in 1950.

Euphoria was observed in four cases, but one patient became more depressed in spite of improvement in joint symptoms. The improvement usually started within an hour and frequently within 15 minutes of the injection, the average duration of response being 18 hours. In suitably conditioned patients later injections of saline reproduced the same response, even to the length of the latent period. In general there was usually a diminished response to further injections, in fact a progressive falling off. Sometimes a good response was followed by rebound aggravation of symptoms probably due to overuse of affected joints. Occasionally later injections resulted in aggravation of symptoms. When the injections lost their effect, the patient sometimes denied that any benefit had ever occurred, although such improvements had been admitted previously. The possibility arose that the psychological response to the injections had activated an endocrine mechanism, which had caused an ACTH like effect. However, the absence of objective evidence of improvement was against this. In addition, in six patients in whom there was a good response, no significant eosinophil decrease was

observed as a result of the injections. There were no overt psychological abnormalities present in any of the patients, and no relation to age, response to previous courses of injections such as gold, or to duration or severity of joint damage, could be established. The marked personal factor involved in placebo response was seen in the following case:

(2) *Female, aged 48*, with a ten-year history of active and progressive disease, had a moderate response in the preceding trial of injections. However, 3½ hours after her first interview with a spiritual healer, she had a remarkable response. This latent period is interesting as the improvement started after she had ceased to expect benefit, illustrating the subconscious nature of the mechanism. Her joint tenderness disappeared; so that, whereas before she was so crippled that she could only walk slowly and with sticks, after the interview she walked quite normally and without pain, and the following day she walked several miles unaided, without apparent ill effect. She continued to visit the spiritual healer and although improvement was maintained for two months, there was a gradually diminishing response and at the end of this time her symptoms had completely relapsed.

Placebo Effects in Ankylosing Spondylitis.—Placebo effects were much less marked in six patients with ankylosing spondylitis who were treated in the same way as the series of rheumatoids. One patient said that his pain was relieved by the injections to the same extent as after an injection of morphia. However, he was not impressed with them as his functional capacity was limited by stiffness and ankylosis and was not affected.

Series of Controlled Cases

When a series of rheumatoid patients were treated with saline injections, followed by injections of DOCA and ascorbic acid under controlled conditions, no appreciable effect on joint tenderness, pain, movement, or performance tests was noted. Neither in these patients nor in normal subjects was any euphoria or effect on appetite produced. The absence of any response, even after the first injections, in these subjective criteria was attributed to the neutral attitude preserved by all concerned in the injection courses, combined with the fact that there was no suggestion that the patients should take particular note of their symptoms. This absence of placebo effect may be correlated with the observation made by Schumacher and others (1940) that the pain threshold in man shows uniformity under standard conditions.

Mechanism of Placebo Response

The mechanism whereby placebos cause subjective improvement in rheumatoid arthritis is a matter for speculation. The link is the reduction of pain, and hence of tenderness, brought about by the patients' subconscious and conscious expectation of improvement. Performance tests, such as walking and making repetitive movements, are limited primarily by pain in many cases, muscle spasm, joint swelling,

ankylosis, contractures, and tendon lesions being limiting factors in others. Thus one patient with ankylosing spondylitis and severe peripheral joint involvement, who had an intelligent insight into his condition, was able to say that before his disease became too advanced, one tablet of codeine compound enabled him to throw away his crutches until the analgesic effect wore off. Many patients in a rheumatism clinic, of course, remark that aspirins enable them to keep going.

The euphoria produced by placebo agents is of considerable interest; it is due to the elimination of pain and its depressing emotional repercussions, together with the patient's conviction that the disease is regressing. It is this latter factor that prolongs the action of placebo effect and makes it more potent than the action of analgesics.

The intensity of the euphoria in a few cases raises the suspicion that its occurrence after cortisone or ACTH therapy may be not altogether a specific effect of these compounds, but largely a reaction to the improvement produced.

Case of Painless Rheumatoid Arthritis

A remarkable preservation of function in the face of severe rheumatoid arthritis was seen recently in a 40-year-old woman; this could only be accounted for by the absence of pain, which in her case characterized the disease. Her wrists, fingers, right elbow, ankles, and feet were actively affected with damage to the bone and soft-tissue swelling, and the erythrocyte sedimentation rate (corrected Wintrobe) was 31 mm. in one hour. The disease had been progressive for 11 years and throughout this time she had worked as a telephonist at a busy exchange and engaged in extra work in her spare time. This work involved continual manipulative movements of the most affected joints, but she had never lost a day's work, being inconvenienced only by joint stiffness and slight joint discomfort, not amounting to pain. Her cutaneous pain threshold, measured after the method described by Hollander (1939), was found to be grossly elevated. A pressure of 250 mm. Hg on a cheese grater placed against the skin evoked only minimal discomfort, as compared with control values of 35, 50, and 20 mm. in normal subjects. The negative history and examination in relation to a wide range of pain-producing situations and stimuli in this patient, showed that although she appeared otherwise normal psychologically and neurologically, she had an apparent constitutional hypo-algesia. In this respect she resembled a patient described by Kunkle and Chapman (1943) and this fortunate trait seemed largely to neutralize the crippling effect of the disease.

Discussion

As criteria of rheumatoid activity, estimates of pain and tenderness provide evidence of a subject nature, and this also applies to joint-range, measurements, performance tests, and grip-meter readings, when pain participates in their limitation.

Accordingly these tests can be altered under circumstances which do not influence the disease process. To avoid any fallacies in the assessment of rheumatoid therapy, the New York Rheumatism Association recommended the strictly objective criteria formulated by Steinbrocker and others (1949) to the exclusion of subjective criteria. This system devised before the advent of cortisone and ACTH has, however, certain disadvantages where rapid assessment of a range of substances is necessary. Firstly, objective signs may be scanty where systemic

signs of the disease are absent or minimal, e.g. cases where there is no elevation of the sedimentation rate. Joint swelling may be slight and is not always easily measured, though here a graded series of rings devised by Dr. Dudley Hart, are of considerable help in proximal interphalangeal joint measurements. One of the N.Y.R.A.'s criteria of an effective remedy is its ability to reduce or eliminate restriction of joint mobility, other than that associated with irreversible change. This association is not easily assessed, and joint range, as has been stated above, is not strictly objective since it can be influenced in many cases by placebo measures. Even serial joint biopsies, the most direct of objective criteria, are not infallible owing to difficulties in taking comparable specimens, a point stressed by Hench (1950).

The advantages of subjective methods of assessment are their ease and simplicity and their universal application, although observer error and daily variations have to be allowed for.

Summary

To avoid interference by psychological factors the following precautions are advisable in therapeutic trials in rheumatic diseases:

(1) The establishment, as far as possible, of a neutral attitude in all concerned with the trials. This cuts out bizarre placebo effects and makes for steady base-line observations, which enable an effective remedy to show its action more strikingly even in a small series.

(2) The use of inert control substances, the identity of which is unknown to patient, observer, nursing staff, and all in contact with the patient.

(3) A preliminary period of observation and assessment during which an in-patient may settle down in hospital and the course and tempo of the disease may be noted under standard conditions.

(4) The simultaneous assessment of all available objective data.

With these precautions, psychological interference is reduced to a minimum, allowing subjective changes to parallel rheumatoid-disease activity, and to be used in its assessment.

I should like to thank Dr. F. Dudley Hart for his encouragement and for permission to report cases from the Rheumatism Unit, Westminster Hospital, Dr. Andrew Bogdan for his help in the work carried out, and Miss F. E. Stevens for all the secretarial work involved.

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Les Facteurs Psychologiques et la Douleur dans l'Évaluation du Traitement du Rhumatisme

Résumé

Pour éviter l'ingérence des facteurs psychologiques au cours des essais thérapeutiques dans les affections rhumatismales on recommande les précautions suivantes:

(1) Créer, autant que possible, une attitude neutrale chez tous les intéressés. Ceci éliminera les effets surprenants chez les témoins et offrira aux observateurs un critère invariable, de manière qu'un remède efficace puisse montrer sa valeur d'une façon frappante même dans un petit nombre des cas.

(2) Utiliser des substances-témoins inertes dont l'identité soit inconnue au malade, à l'observateur, aux infirmières et à tous ceux qui approchent le malade.

(3) Instituer une période préliminaire d'observation et d'évaluation; pendant que le malade s'adapte à la vie à l'hôpital on notera la marche et le tempo de l'affection dans des conditions standard.

(4) Evaluer simultanément toutes les données subjectives disponibles.

Ces précautions réduisent au minimum l'ingérence psychologique ce qui permet dans l'évaluation de tenir compte des signes subjectifs se manifestant en fonction de l'activité rhumatismale.

Factores Psicológicos y Dolor en la Valoración de la Terapia Antirreumática

Resumen

Para evitar la interferencia de factores psicológicos las siguientes precauciones son recomendables durante pruebas terapéuticas en casos de enfermedades reumáticas:

(1) Establever en lo posible una actitud neutral en todos los interesados en las pruebas. Eso permite eliminar los efectos sorprendentes que se suele ver con las substancias de control y ofrece una línea de mira fija las observaciones. De esta manera, un remedio eficaz puede manifestar su acción en forma destacada hasta en un pequeño número de casos.

(2) Usar, para el control, substancias inertes cuya identidad debe ser desconocida para los pacientes, observadores, personal clínico y todos aquellos en contacto con los enfermos.

(3) Crear un período preliminar de observación y de valuación durante el cual el paciente pueda adaptarse a la vida hospitalaria, y el curso y marcha de la enfermedad puedan ser observados bajo condiciones estandardizadas.

(4) La valoración de todos los datos objetivos disponibles debe realizarse simultáneamente.

Con estas precauciones, la interferencia psicológica se reduce al mínimo, los signos subjetivos se manifestan en función de la actividad reumática y pueden servir así para la valoración.

"EXPERIMENTAL ERROR" OF THERAPEUTIC TRIALS IN RHEUMATOID ARTHRITIS

BY

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In trials of substances alleged to cause rapid improvement, or to have a cortisone- or ACTH-like action in rheumatoid arthritis, it is necessary to determine the "error range" of the method of observation to be employed. If the degree of "experimental error" be known, a base-line exists for further observations. Without this knowledge, it is impossible to assess the significance of results of trials of therapeutic substances.

This paper reports an experiment, involving no treatment whatever, on patients suffering from rheumatoid arthritis, using the method of serial clinical assessments. Its purpose is to demonstrate that this method carries too gross an "experimental error" to be useful in therapeutic trials unless strict statistical control be imposed at all stages.

Material

Eight women with typical advanced rheumatoid arthritis were selected for study. Their ages ranged from 51 to 78 years and they had suffered from the disease for 5 to 34 years. They had been in hospital continuously for from 7 months to 4½ years. Only one was bedridden but none could walk unassisted. The criteria for selection were:

willingness and mental ability to co-operate in the trial;
symptoms and signs typical of chronic rheumatoid arthritis in relapse, with pain at rest, aggravated by movement or pressure;
inability to demonstrate a specific aetiology;
erythrocyte sedimentation rate above 25 mm. in 1 hour (Westergren);
anaemia;
malaise;
radiographic appearances characteristic of the disease.

Method

The nature of the experiment was explained to each patient individually. During the trials they received no treatment whatever. They were closely questioned and examined by the same observer, at different times and in different wards, at hourly intervals for 8 hours and then at 12 and 24 hours. Serial hourly observations were repeated on three different occasions on all eight patients, making a total of 24 experiments.

The questions and examination followed a set routine. At "zero hour" they were asked how they felt "generally", and to put their pain into one of the categories slight,

moderate, or severe. The range of movement in both elbows and both knee joints was measured by goniometer, and the mean of all four joints recorded in degrees.

At each subsequent observation, the range of joint movement was recorded after putting the questions:

(1) " generally ", do you feel better, worse, or has there been no change since the last time ? and (if applicable), much or little ?
(2) Is the pain better, worse or unchanged, and (if applicable), is it now nil, slight, moderate, or severe ?

Results

The results are shown in the Table. All the patients showed semeiological variation in at least one experiment. Change was usually apparent at the first hour, reached a maximum between 2 and 6 hours, and had subsided by the 24th hour (see Figure). The three modalities observed (i.e. pain, range of movement, and " general feeling ") always changed in the same direction, though not to the same degree.

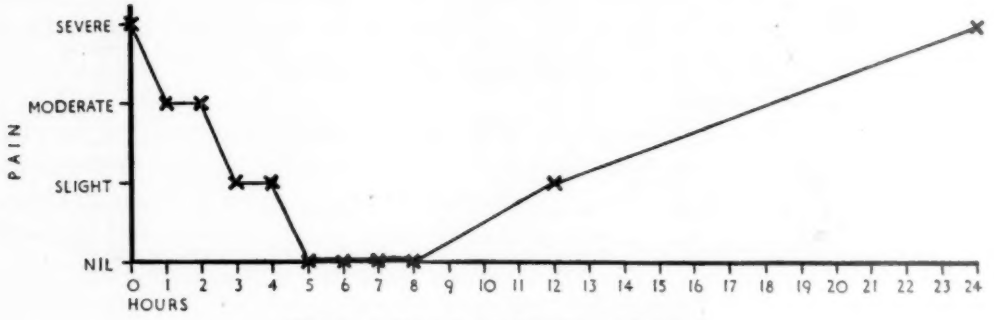

FIGURE.—Case 5, results of experiment 1.

General.—Maximal general improvement occurred in two instances (from " I feel very poorly " to " I feel better now than I've done for months "); considerable change was recorded in fifteen.

Pain.—In four instances the alteration in pain was maximal (i.e. between nil and severe); in eleven, considerable variation occurred; in two, pain changes were slight.

Movement.—The variation in range of painless movement was as much as 15° in six cases, and between 5° and 15° in eleven.

As the Table shows, notable changes occurred in seventeen (70 per cent.) of the 24 serial assessments:

improvement in twelve (50 per cent.),
deterioration in three (12·5 per cent.),
hour-by-hour vicissitudes in two (8·5 per cent.).

In seven experiments (30 per cent.) no notable change was observed.

TABLE

RESULTS OF EXPERIMENTS IN EIGHT CASES

Case No.	Experiment 1			Experiment 2			Experiment 3		
	General	Pain	Movement	General	Pain	Movement	General	Pain	Movement
1	B+++	B++	B 12	B++	B+++	B 15	B++	B++	B 10
2	N	N	N	N	N	N	B++	B+	B 7
3	V++	V++	V 15	W++	W++	W 11	B++	B++	B 10
4	B++	B+	B 5	N	N	N	N	N	N
5	B++	B+++	B 15	W++	W++	W 5	B++	B++	B 7
6	N	N	N	V++	V++	V 13	W++	W+++	W15
7	N	N	N	N	N	N	B+++	B+++	B 15
8	B++	B++	B 10	B++	B++	B 15	B++	B++	B 11

Key. B = progressive improvement.
V = vicissitudes.
W = progressively worse.
N = no change.

General Change expressed as: N = nil or slight.
++ = considerable.
+++ = remarkable.

Pain Change expressed as *difference* between: severe (+++)
moderate (++)
slight (+)
nil (0)
e.g. severe to slight = ++ (+++ minus +).

Movement Change expressed in degrees: N = less than 5° change.

Discussion

Such may be called the experimental error of the method of serial clinical assessments. It is compounded of:

(1) the crudeness of methods of measuring range of movement, etc.;

(2) individual variation in the patient's suggestibility to

(*a*) the personality of the examiner,
(*b*) the act of being observed,
(*c*) the manoeuvres entailed;

(3) variation from hour to hour in the patient's standard of pain, etc.;

(4) unconscious bias in the examiner;

(5) wish of the kindly patient to please, or of the " difficult " patient to impress;

(6) genuine fluctuations, by the hour, in the mood and symptoms of a patient with chronic rheumatoid arthritis in exacerbation.

This " experimental error " is so great that conclusions other than those based on large numbers of experiments, statistically controlled and analysed, are invalid.

This method was chosen for study as it is the one most commonly used in clinical practice; yet its fallacies are not generally realized.

The deoxycortone-ascorbic acid polemic initiated by Lewin and Wassén (1949) included contributions by able clinicians; but no observer, however skilful, can measure accurately without knowing the length of his measure. With few exceptions (Bywaters and others, 1950; Spies and others, 1949; Quin and others, 1950) neither protagonists* nor antagonists† planned their trials so as to take into account the wide range of error in uncontrolled serial clinical assessments of rheumatoid arthritis.

The methods of Copeman and others (1950b) or of Quin and others (1950) are far more appropriate for therapeutic trials, and future studies should be modelled upon them.

Summary

A study of eight elderly women with chronic rheumatoid arthritis in relapse is reported.

Although no treatment was given, the incidence of hour-by-hour variation in symptoms and signs was high, and the extent of change considerable.

The reasons for these variations are analysed.

Because of the large " experimental error ", the method of serial clinical assessment without statistical control and analysis, is unsuitable for therapeutic trials.

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† Copeman and others (1950a), Currie and Will (1950), Fletcher and others (1950), Hartfall and Harris (1949), Kellgren (1949), Kersley and others (1950).

" Erreur Expérimentale "
dans les Essais Thérapeutiques de l'Arthrite Rhumatismale

RÉSUMÉ

Huit femmes âgées atteintes d'arthrite rhumatismale chronique furent soumises à cette étude.

Bien qu'elles n'aient reçu aucun traitement, la fréquence des variations des symptômes et des signes d'heure en heure était grande et l'amplitude des altérations considérable.

L'auteur analyse les raisons de ces variations.

À cause de la forte " erreur expérimentale ", la methode qui consiste à grouper les résultats cliniques sans les soumettre au contrôle statistique et analytique ne convient pas à l'évaluation des données des essais thérapeutiques.

" Error Experimental "
en las Pruebas Terapéuticas de la Artritis Reumatoide

RESUMEN

Ocho mujeres de edad avanzada, con artritis reumatoide crónica, fueron sometidas a este estudio.

Aunque no recibieron tratamiento alguno, la frecuencia de las variaciones por horas de los síntomas y de los signos fué grande y la latitúd de las alteraciones considerable.

Se analiza las razones de estas variaciones.

En vista del gran " error experimental ", el método de agrupar los resultados clínicos sin someterlos al control estadístico y analítico no conviene a las pruebas terapéuticas.

HOMOLOGOUS TISSUE SENSITIZATION

FAILURE TO PRODUCE JOINT AND KIDNEY LESIONS OR PRECIPITINS WITH HOMOLOGOUS TISSUES PLUS STREPTOCOCCI*

BY

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Atrophic arthritis has been produced experimentally in animals, but not under conditions comparable to those observed in man. Study of the disease has thus been handicapped. Homologous tissues plus adjuvants have been used successfully to produce organ-specific lesions in the kidneys (Klinge and Knepper, 1935; Schwentker and Comploier, 1939; Cavelti and Cavelti, 1945a, b, c; Sprunt and others, 1950); in the central nervous system (Kopeloff and Kopeloff, 1944; Kabat and others, 1947; Morgan, 1947); in the heart, skeletal muscle, and connective tissues (Cavelti, 1945; 1947). This paper summarizes unsuccessful attempts in 1946-48:

(1) to produce arthritis in guinea-pigs and rats by injecting homologous joint tissues plus haemolytic streptococci;

(2) to repeat the production of renal lesions by injecting homologous kidney tissues plus haemolytic streptococci (Cavelti and Cavelti, 1945a, b, c; Cavelti, 1945; 1947).

These unsuccessful experiments are reported now because others (Peck and Thomas, 1948; Humphrey, 1948) have been unable to confirm the report of renal lesions by similar methods.

Method

Guinea-pigs, 400-500 g., were used in the first experiment because they are so susceptible to anaphylactic sensitization. Rats, 200-300 mg., were used in a second experiment, because they had been used successfully by Cavelti and Cavelti.

Antigens were prepared essentially as described by Cavelti and Cavelti (1945a, b, c). Joint tissues and kidneys were removed, aseptically, from anaesthetized animals which had been perfused with saline to remove the blood. Each type of tissue was emulsified in about 6 vols saline in a Waring blender. Four parts of each tissue emulsion, proved sterile by culture, were mixed with one part of a 4 per cent. saline suspension of washed, heat-killed virulent β haemolytic streptococci. All mixtures were kept frozen at $-4°$ C. until the time of injection.

Twenty-four guinea-pigs were injected every other day for nine doses. The doses were 0·1, 0·2, 0·4, 0·6, 0·8, 1·0, 1·0, 1·0, and 2·0 ml., a total of 7·1 ml. Twelve animals were given articular tissue plus streptococci, and twelve were given kidney emulsion plus streptococci.

Seven weeks after the last injection all of the animals remained perfectly well. Eight were re-injected with a total of 4·1 ml. of the same antigens in three doses in 5 days. There were no detectable immediate or delayed local or general reactions to the second series of injections. Four received kidney plus streptococci, four received joint tissue plus

* These studies were made possible by a grant from Ciba, Summit, N.J., U.S.A.

streptococci, and these were killed 2 weeks after the last injection. The other sixteen were killed at the same time, 10 weeks after their first and only series of injections.

Twelve rats were injected with a total of 15 ml. joint emulsion plus streptococci, and twelve were given the same amount of kidney emulsion plus streptococci. The doses were 2·0 ml. daily for 5 days, then 5·0 ml. on the 6th day. The animals were killed 3 weeks after the last injection.

The kidneys, knee joints, and hearts were removed from the guinea-pigs and rats, and immediately preserved in formalin.

Controls included untreated guinea-pigs and rats, and rats given kidney emulsion, joint emulsion, or suspensions of streptococci.

Results

No anti-kidney or anti-articular precipitins were demonstrated by the J-tube technique (Pearsall and others, 1945). The collodion-particle method was not used, its value being doubtful unless sterile techniques are employed (Swineford and others, 1947).

Frequent urine analyses showed no more than an occasional cell or trace of albumin in the guinea-pigs and rats treated with kidney emulsion plus streptococci.

X-ray and physical examinations of the joints of the animals treated with joint emulsion plus streptococci showed no evidence of joint involvement.

Histologic study of the kidneys, joints, and hearts of the experimental guinea-pigs and rats were indistinguishable from those of the controls.

Summary

The production of pathological changes in the joints and kidneys of guinea-pigs and rats was attempted by injecting homologous tissue emulsions plus streptococci. Neither antibodies, urinary changes, nor histological changes were demonstrated.

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Sensibilisation par Tissus Homologues
Tentatives infructueuses de produire des lésions rénales et articulaires ou des précipitines par injections des tissus homologues avec des streptocoques

Résumé

L'injection des émulsions des tissus homologues avec des streptocoques aux cobayes et aux rats n'a pas produit de modifications pathologiques dans les articulations ni dans les reins. Ni des anticorps, ni des modifications urinaires ou histologiques ne furent décelés.

Sensibilización por Tejidos Homólogos
Tentativas infructuosas de producir lesiones renales y articulares o precipitinas mediante inyecciones de tejidos homólogos con estreptococos

Resumen

Inyección de emulsiones de tejidos homólogos con estreptococos a cobayos y ratas no llegó a producir alteraciones patológicas de las articulaciones ni de los riñones. Anticuerpos, modificaciones urinarias o alteraciones histológicas no fueron encontrados.

CALCIUM SUCCINATE WITH ASPIRIN IN THE TREATMENT OF RHEUMATIC DISEASE

(I) A CLINICAL EVALUATION*

BY

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" Dolcin " is composed of calcium succinate 2·5 gr. with aspirin 3·9 gr. The supposed action of the calcium succinate is to increase tissue oxygenation and thereby to increase the action of the aspirin (*Bureau Invest.*, 1949). Szucs (1947) claimed that succinic acid has a stimulating effect on cellular respiration and protects tissues against impairment of cellular respiration. He believed that the combination of succinic acid with salicylates in proper doses and proportions is more effective and better tolerated than salicylates alone.

In November, 1947, we were given the opportunity to make a clinical evaluation of this drug at the Arthritis Clinic of the Newark Presbyterian Hospital in Newark, New Jersey.

Method

Dolcin was administered according to manufacturer's recommendations (see p. 121 below). After several months of this routine, we substituted another tablet which had the exact appearance of Dolcin, including the raised letter " D " as on the Dolcin tablet, but containing only 3·9 gr. aspirin and no calcium succinate. The patients were unaware that they were taking not D (Dolcin) but D control, as we called the aspirin tablet. No other medication was given. Several patients who had been on physical therapy had to be started again in order not to lose them from the study.

Before beginning clinical analysis all cases underwent a re-evaluation of their arthritic status by complete physical examination, *X*-ray examination, and laboratory studies. These included a complete blood count, urine analysis, sedimentation rate, blood chemistries such as uric acid, non-protein nitrogen, and cholesterol. All cases studied were seen at random by all the workers in the clinic to eliminate personal reactions. Numerous rechecks, *x* rays, and laboratory studies were done throughout the survey. Several patients who were given Dolcin, but stopped after a short time, are not included in the study.

* Sponsored by the American Rheumatism Association Committee on Affiliation with the Food and Drug Administration.

Case Reports

Case 1. C.G., 58-year-old female, suffering from post-menopausal osteo-arthritis of the knees, of 8 years' duration, and obesity. *X* rays showed osteo-arthritic lipping of the knees. All laboratory findings were normal except the erythrocyte sedimentation rate which was 19 (Cutler method). She was treated on Dolcin and D control from January 16, 1948, to November 5, 1948. There were periods of relief with both therapies. The patient stated that much more relief was afforded by loss of weight, proper shoes, and support to the knees, than by the Dolcin treatment.

Case 2. E.H., 64-year-old female, suffering from osteo-arthritis of the hands with osteo-porosis of 3 years' duration. All laboratory findings were normal. This patient had been taking 10 gr. sodium salicylate every 3 hours with fair results. This was stopped for one month and with return of symptoms Dolcin was started on January 9, 1948. The patient experienced relief from pain, but no increase of functions. She was then switched to D control and after several months the condition was unchanged. She still had relief from pain but the stiffness of the metacarpal-phalangeal joints of the right hand continued. She left the neighbourhood while on D control on September 10, 1948, and has not been seen since.

Case 3. J.B., 58-year-old female, weight 283½ lb. (over 20 st.), suffering from osteo-arthritis of both knees, of 12 years' duration. All laboratory findings were normal. Sodium salicylates 10 gr. every 3 hours was started on December 12, 1947. On January 9, 1948, she was changed to Dolcin, with no change in condition. When her weight increased, by February 20, 1948, to 287 lb., she was told that unless she adopted a weight-reducing diet we would not continue therapy, and she was not seen after this, but her condition both subjective and objective was unchanged by the six weeks' treatment.

Case 4. M.C., 54-year-old female, weight 92 lb. (6½ st.), suffering from rheumatoid arthritis, which had begun 7 years before with rheumatoid changes in hands and knees. She was placed on sodium salicylate 10 gr. every 4 hours with good relief from pain. Because of enlarged cervical glands and a persistent leucocytosis of over 20,000 with marked lymphocytosis, the possibility of lymphatic leukaemia was considered and bone-marrow studies were done. The findings were suggestive of lymphatic leukaemia and we were advised to watch her.

After an examination in December, 1947, *x* rays were taken which showed marked rheumatoid changes in both wrists, and ankylosis and erosion of the distal ends of the ulnas. The laboratory findings were as follows:

Haemoglobin: 88 per cent.
Red blood count: 4,400,000.
White blood count: 30,650.
Differential: lymphocytes 80 per cent.; polymorphonuclears 20 per cent.
Non-protein nitrogen: 28.
Blood sugar 110 mg.
Uric acid 4 mg.

Dolcin was started on January 4, 1948, sodium salicylate having been discontinued in September, 1947. The patient felt considerably improved except for a flare-up of rheumatoid arthritis in March and April, 1948. On October 22, 1948, D control was started. In March, 1949, while she was still on D control, improvement began and continued until April 29, 1949, when another exacerbation of rheumatoid arthritis occurred. The general condition of the patient was unchanged.

Case 5. J.S., 60-year-old female, weight 103½ lb. (about 7½ st.), suffering from generalized osteo-arthritis. She was referred to the arthritis clinic for pains of 10 years' duration in hands, knees, and cervical spine. All laboratory findings were normal. The patient was started on Dolcin on January 9, 1948, and the response was similar to that experienced with sodium salicylate. She took Dolcin until May, 1948, when it was

stopped because of abdominal cramps. Dolcin was started for another month on September 24, 1948, and then stopped again. On November 19, 1948, after a month's rest, D control was started and the patient now stated that her relief from pain was greater. On April 21, 1949, she developed cramps in the legs which may have been due to intermittent claudication, and was referred to the cardiac clinic.

Case 6. S.P., 67-year-old male, suffering from osteo-arthritis of knees and Parkinson's disease. All laboratory findings were normal. On January 16, 1948, he was started on Dolcin. On January 30, 1948, he still felt no improvement. On May 28, 1948, he stated that he "felt terrible", and complained of gas, heartburn, and constant pain, stating that "pills don't help at all". The haemoglobin dropped and the sedimentation rate increased while on Dolcin, and the patient, feeling no better, refused to continue Dolcin or D control.

Case 7. J.W., 69-year-old male, suffering from destructive osteo-arthritis of the right hip. He felt better at times on various regimes, such as deep *x*-ray therapy, foreign protein, salicylates, local procaine, crude liver, physical therapy, and prostigmin. Dolcin was started on February 13, 1948, with mild subjective improvement at first, but with no objective improvement. After changing to D control, there was continued subjective improvement until October 8, 1949, when pains in the right hip recurred and D control was stopped.

Case 8. X.Y., 66-year-old female, suffering from osteo-arthritis of the lumbar vertebrae with pain which radiated from the left hip to the ankle. All laboratory findings were normal. Previous therapies had included diathermy, foreign protein, and Vitamin B complex, all with moderate remission but never with complete clearing of pain. *X* ray examination in December, 1947, showed no change. On February 20, 1948, she was started on Dolcin, and there was no response up to October 15, 1948. Then she refused to start D control as Dolcin did "no good".

Case 9. A.L., 72-year-old female, suffering from osteo-arthritis of both hips and lumbo-sacral joints, with severe pain in the lumbar area of 10 years' duration. She improved on neither Dolcin nor D control, from January 7, 1949, to October 23, 1949, and medication was therefore stopped. There was gastric irritation from both Dolcin and D control.

Case 10. M.R., 64-year-old female, suffering from osteo-arthritis with lipping of external condyle of right tibia. All laboratory findings were normal. On June 25, 1948, Dolcin was started, and she felt better at first but later the pains recurred. On October 14, 1948, D control was started and no difference in reaction resulted. By May 27, 1949, there was no change in her condition.

Case 11. H.S., 72-year-old female, suffering from osteo-arthritis of hips and knees. All laboratory findings were normal. On February, 1949, she was started on D control with no effect, and on June 24, 1949, she was started on Dolcin, also with no effect. She was replaced on D control on August 25, 1949, and when there was still no effect all therapy was stopped on October 23, 1949.

Case 12. W.S., 58-year-old male, suffering from rheumatoid spondylitis of 6 years' duration. Dolcin was started on January 9, 1948, without any effect. As the patient was in severe pain, *x*-ray therapy was instituted in August, 1949, and on September 16, 1949, D control was started, but it was stopped on October 21, 1949, as there was still no change in his condition.

Summary

(1) During a two-year period, the action of "Dolcin" (a proprietary tablet containing aspirin 3·9 gr. and calcium succinate 2·5 gr.) was compared with that of aspirin alone in doses similar to that contained in the tablets.

(2) A complete course of treatment was given as recommended by the

manufacturer, and its effect compared with that of aspirin alone given by a similar course in similar doses.

(3) Although " Dolcin " often gave relief from pain, the relief was symptomatic only, and the patient was no better than when aspirin was given alone.

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Evaluation Clinique de " Dolcin "

RÉSUMÉ

(1) Pendant une période de deux ans, l'action de " Dolcin " (spécialité médicale de comprimés contenant de l'aspirine 3·9 gr. et du succinate de calcium 2·5 gr.) fut comparée à celle de l'aspirine seule en doses similaires.

(2) On soumettait les malades à une cure complète selon les instructions des fabricants et on comparait l'effet à celui obtenu par une cure similaire d'aspirine seule en doses similaires.

(3) Bien que " Dolcin " faisait souvent diminuer la douleur, le soulagement n'était que symptômatique et le malade ne se portait pas mieux que quand il prenait de l'aspirine seule.

Valoración Clinica de " Dolcin "

RESUMEN

(1) Durante un período de dos años la acción de " Dolcin " (específico en forma de comprimidos conteniendo aspirina 3·9 gr. y sucinato de calcio 2·5 gr.) fué comparada a la de aspirina sola en dosis similar a aquella contenida en los comprimidos.

(2) Los enfermos fueron sometidos a un tratamiento completo según la recomendación del fabricante y los efectos comparados con aquellos de la aspirina sola, administrada de manera semejante y en dosis similares.

(3) Aunque " Dolcin " frecuentemente calmó el dolor, el alivio fué meramente sintomático y los enfermos no se sintieron mejor que cuando tomaron simplemente aspirina.

(II) CALCIUM SUCCINATE WITH ASPIRIN AS AN ANTI-RHEUMATIC AGENT*

BY

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A clinical evaluation of " Dolcin " (calcium succinate 2·5 gr. with aspirin 3·9 gr., see p. 118) was conducted in the Rheumatology Clinic in the Out-Patient Department of the Georgetown University Hospital between August, 1948, and August, 1949. Four cases of rheumatoid arthritis and five cases of osteo-arthritis were given this drug in accordance with the manufacturer's instructions:

> IT IS RECOMMENDED that not fewer than TWELVE tablets be taken daily (three tablets with water before each meal, and three at bedtime) until acute symptoms are relieved. Then, follow this with EIGHT TABLETS (two tablets, four times) daily for ten weeks . . . or until all symptoms disappear. At this time, cut the dosage to FOUR TABLETS (one tablet, four times) for eight weeks more.

* Sponsored by the American Rheumatism Association Committee on Affiliation with the Food and Drug Administration.

For the most effective results it is most important to continue taking the tablets for a few months after relief from pain has been obtained, for it is an established fact that Rheumatic activity usually persists in the body for a considerable period after the acute symptoms have subsided.

In addition, four cases of rheumatoid arthritis and four cases of osteo-arthritis were given a placebo of the exact appearance of Dolcin (including the raised letter " D " similar to that on the tablet), but containing only 3·9 gr. aspirin.

Patients who were receiving placebo were given the same instructions as those receiving Dolcin. Medications given to the patient were designated " AB-1 " and " CD-2 ". It was not known to the patient nor to the physician administering the drug which of these two medications was Dolcin and which was aspirin alone until the completion of the test. No other medications were given during the test.

Cases were selected at random from those referred to the Rheumatology Clinic. Prior to the institution of therapy, all patients underwent a complete medical survey including history, physical examination, complete blood count, urine analysis, sedimentation rate, and *x* ray of at least one involved joint. The author personally reviewed each case before and at the completion of therapy. All the cases of rheumatoid arthritis chosen for the study showed evidence of rheumatic activity as indicated by symptoms of pain and stiffness, and one or more objective signs of tenderness, swelling, limitation of motion, redness and local heat, plus an elevated sedimentation rate. The cases of osteo-arthritis presented symptoms of pain and stiffness, and jelling phenomena, signs of chronically enlarged joints with limitation of motion in some cases, and *x*-ray evidence of hypertrophic lipping and spur formation.

Each case was evaluated on the alleviation or increase of subjective symptoms, the alteration of objective signs, and changes in laboratory data during and at the conclusion of the test.

Case Reports

A. Rheumatoid Arthritis Cases receiving Dolcin.

(1) G.E., 60-year-old white female, with rheumatoid arthritis of 30 years' duration, was given Dolcin from November 4, 1948, to May 19, 1949. During that time there was some moderate subjective improvement with relief of some of the soreness and pain, and slight objective improvement with increased range of motion. There was no change in the sedimentation rate which remained elevated and no change in the *x*-ray appearances.

(2) C.T., 48-year-old white female, with rheumatoid arthritis of two years' duration, was given Dolcin from December 22, 1948, to March 23, 1949, during which time there was no objective improvement, and the patient felt somewhat worse subjectively. There was no change in the sedimentation rate nor in the *x*-ray appearances.

(3) Ch.T., 72-year-old white male, with rheumatoid arthritis of ten months' duration, was given Dolcin from August 12, 1948, to October 28, 1948, during which time he went downhill rather markedly both subjectively and objectively, with increasing pain and limitation of motion of the involved joints. During this period he also developed gastro-intestinal upset with reactivation of an old duodenal ulcer which had been inactive for some months prior to therapy. There was no change in either the sedimentation rate or the *x*-ray appearances. After ten weeks the patient felt so bad that he refused to continue the medication.

(4) J.C., 53-year-old white female, with rheumatoid arthritis of nine years' duration, was given Dolcin from May 12, 1949, to July 21, 1949. During the last two weeks

of therapy the patient noted some moderate subjective improvement with some relief of soreness, but there was no objective improvement, neither increased motion nor decreased swelling. There was no change in the sedimentation rate nor in the *x*-ray pictures.

Thus, of the four cases of rheumatoid arthritis treated with Dolcin, two (G.E. and J.C.) noted some subjective improvement, and two others (C. T. and Ch. T.) felt worse while taking the drug. The only objective changes were some slight increase in the motion of some of the involved joints in one (G.E.) and moderate increase in the acute swelling with decreased motion of the joints in another (Ch. T.). There was no significant change in the *x*-ray appearances or sedimentation rate in any case.

B. Rheumatoid Arthritis Patients receiving Placebo.

(1) L.B., 49-year-old white female, was given the placebo from August 26, 1948, to March 17, 1949, during which time there was initial improvement but then steady progression of symptoms. At the conclusion of therapy there was no significant subjective nor objective change; the sedimentation rate remained elevated and there was no change in the *x*-ray appearances.

(2) W.J., 66-year-old coloured male, had had recurring attacks of rheumatoid arthritis for some 40 years. He was given the placebo from February 3 to July 9, 1949, during which time there was moderate subjective improvement but no objective change. The sedimentation rate remained elevated and the *x* rays showed no change.

(3) M.P., 39-year-old white female, with rheumatoid arthritis of some 20 years' duration, was given the placebo from October 14, 1948, to January 27, 1949. There was progression of the symptoms during that time, and the sedimentation rate, which was normal at the start of therapy, was markedly elevated at the completion. *X* rays showed some moderate increase in the condition.

(4) M.T., 39-year-old coloured female, with progressive rheumatoid arthritis of 4 years' duration, was given the placebo between September 16, 1948, and December 2, 1948. During this time she went progressively downhill clinically, but the sedimentation rate fell from 60 to 41. There was no significant change in the *x* rays.

Thus, of the four cases taking the placebo, one (W.J.) claimed some subjective improvement and two (M.P. and M.T.) felt worse. The two latter showed objective clinical signs of increased progress of the disease, although one (M.T.) showed a fall in the sedimentation rate and the other a rise. The *x* rays showed little change.

Of interest is the fact that all eight cases of rheumatoid arthritis were asked to stay on the drug at least five months, but only one of the cases taking Dolcin and two of the cases taking the placebo would do so, the others refusing on the grounds that they were not being benefited. However, only a single case of pronounced gastric irritation was noted, a reactivation of an old ulcer in one of the cases taking Dolcin.

C. Osteo-Arthritis Cases receiving Dolcin.

(1) A.B., 62-year-old coloured female, had exhibited symptoms for only three years, but her marked *x*-ray changes indicated the existence of the condition over a considerably longer period. She took Dolcin from October 7, 1948, to April 21, 1949, with rather marked subjective relief of pain and soreness, and moderate objective evidence of increased motion. No change in the *x*-ray picture was noted.

(2) M.G., 58-year-old white female, with symptoms of osteo-arthritis of 10 years' duration, took Dolcin from August 26, 1948, to February 26, 1949. Subjectively there was relief of pain and objectively there was some moderate objective improvement

in the motion of one knee and hand. The relief of pain and stiffness, however, was noted only so long as she was under the influence of the drug and symptoms returned when it was discontinued. The objectively improved motion, however, continued to be noted several months after the drug was discontinued.

(3) C.H., 60-year-old white female, with symptoms of five years' duration, was given Dolcin from September 2, 1948, to March 3, 1949. She had relief of pain so long as the drug was continued, but noted the return of pain and stiffness as soon as it was withheld. There was no objective evidence of any change, but *x* ray of the knees, however, showed a definite increase in the osteo-arthritic lipping several months after the completion of the treatment.

(4) M.S., 64-year-old white female, with symptoms of osteo-arthritis of 10 years' duration, took Dolcin from August 12, 1948, to November 14, 1949, and during that time had marked subjective increase in pain and stiffness with some objective increase in her inability to get up and sit down. *X* rays showed no particular change after therapy.

(5) B.P., 43-year-old white female, who had had symptoms in the hands for approximately 10 years, took Dolcin from August 20, 1948, to April 28, 1949. During that time there was an increase in symptoms, no change objectively, and no change in the *x*-ray appearances.

Thus, of the five cases of osteo-arthritis receiving Dolcin, three (A.B., M.G., and C.H.) noted subjective improvement and two (A.M. and M.G.) were observed to have objective improvement. Two cases (M.S. and B.P.) were subjectively worse, and one (M.S.) was objectively worse. In four there was no change in the *x*-ray picture, and in one there was increased lipping.

D. Osteo-Arthritis Cases receiving Placebo.

(1) B.H., 83-year-old white male, who had had symptoms of osteo-arthritis for about 3 years, was placed on the placebo from October 21, 1948, until April, 1949. He noted marked subjective relief of pain while taking the drug, but there was only moderate objective evidence of any change. *X* rays showed no changes.

(2) V.L., 68-year-old white female, with symptoms of osteo-arthritis of the hands of fifteen years' duration, took the placebo from September 16, 1948, to October 28, 1948, during which time there was increase of pain in the hands and the drug was discontinued because of marked gastro-intestinal upset while it was being taken.

(3) C.S., 67-year-old coloured female, who had had symptoms of osteo-arthritis of the knees for approximately 4 years, took the placebo from October 28 to December, 1948. She noted some relief from pain, but had considerable nausea while taking the drug, and it was therefore discontinued. There was no objective change.

(4) J.S., 57-year-old coloured female with symptoms of osteo-arthritis of the spine of 3 months' duration. *X* rays showed changes which indicated that the process had been present for a considerably longer period. She took the placebo from August 19, 1948, to April 21, 1949. There was some temporary subjective improvement during the first two months of therapy which was not noted thereafter.

Thus, of the four cases of osteo-arthritis who took aspirin alone, two (V.L. and C.S.) noted subjective improvement, but only one showed objective improvement. No significant *x*-ray changes occurred. Two cases developed marked gastric upset.

Summary

(1) Of nine cases of arthritis (four of rheumatoid and five of osteo-arthritis) taking " Dolcin " in accordance with the manufacturer's instructions, five claimed subjective improvement with some relief of pain, four stated that they were worse,

one showed slight and two moderate objective improvement in motion, and one showed lessened motion. No significant alteration in laboratory findings occurred except increased lipping which was seen in the *x* ray in one case.

(2) Of eight cases of arthritis (four of rheumatoid, and four of osteo-arthritis) taking a placebo resembling Dolcin but containing only aspirin, three claimed subjective improvement with some relief of pain, three felt worse, and one noted little change; one showed some slight increase and two decrease in motion. No significant alteration in laboratory findings were observed, except a fall in the sedimentation rate in one case and a rise in one other.

(3) The only toxic reactions noted were the reactivation of an old duodenal ulcer in one case receiving Dolcin and marked gastric irritation in two cases receiving the placebo.

(4) It is concluded that " Dolcin " is not an effective remedy for the treatment of rheumatoid or osteo-arthritis and has no advantage over aspirin alone.

" Dolcin " comme Agent Anti-rhumatismal

RÉSUMÉ

(1) Neuf malades—quatre avec arthrite rhumatismale et cinq avec ostéo-arthrite—furent traités par " Dolcin " selon les indications du fabricant. Cinq d'eux affirmèrent qu'il se sentaient mieux et que leur douleur avait diminué un peu et quatre autres déclarèrent qu'ils étaient plus mal. On constata une amélioration objective du mouvement dans trois cas—légère dans un cas et modérée dans deux cas. Dans un cas la mobilité était diminuée. L'examen de laboratoire ne révéla pas de changements appréciables, saufl'hypertrophie osseuse marginale vue à la radiographie dans un cas.

(2) Huit malades—quatre avec arthrite rhumatismale et quatre avec ostéo-arthrite—furent traités par une substance ayant l'apparence de " Dolcin " mais ne contenant que de l'aspirine. Trois d'eux affirmèrent qu'il se sentaient mieux et que leur douleur avait diminué, trois autres qu'ils étaient plus mal et un d'eux ne nota pas de différence. L'amplitude du mouvement était légèrement améliorée chez l'un d'eux et empirée chez deux autres. A l'examen de laboratoire on ne vit pas de modifications appréciables, sauf que la vitesse de la sédimentation globulaire était augmentée dans un cas et diminuée dans un autre.

(3) Comme réaction toxiques, on ne nota que la réactivation d'un vieux ulcère duodénal chez un sujet qui prenait de la " Dolcin " et une irritation gastrique prononcée chez deux sujets traités par la substance-étalon.

(4) L'auteur conclut que " Dolcin " n'est pas un remède efficace contre l'arthrite rhumatismale ou contre l'ostéo-arthrite et que ce produit ne présente aucun avantage sur l'aspirine seule.

" Dolcin " como Agente Antirreumático

RESUMEN

(1) Nueve enfermos—cuatro con artritis reumatoide y cinco con ósteoartritis—fueron tratados con " Dolcin " de acuerdo con las instrucciones del fabricante. Cinco de ellos afirmaron mejoría subjetiva con cierta disminución del dolor y cuatro otros manifestaron haber empeorado. Se vió un mejoramiento objetivo de la movilidad en tres casos—ligero en un caso y moderado en dos otros. En un caso la movilidad había disminuido. La investigación de laboratorio no reveló cambios apreciables con excepción de hipertrofia ósea marginal vista en la radiografía de un caso.

(2) Ocho enfermos—cuatro con artritis reumatoide y cuatro con ósteoartritis—fueron tratados con una substancia de apariencia similar al " Dolcin " pero que consistía simplemente de aspirina. Tres de los casos dijeron que estaban mejor, con disminución del dolor; tres otros se sintieron empeorados y uno no notó cambio alguno. La amplitud del movimiento fué algo aumentada en un caso y disminuida en otros dos. En la investigación de laboratorio no se observaron alteraciones significantes, con excepción de la sedimentación eritrocitaria, que fué más rápida en un caso y más lenta en otro.

(3) Como únicas reacciones tóxicas se notó la reactivación de una antigua úlcera duodenal en un sujeto al que se administró " Dolcin " y una marcada irritación gástrica en dos casos que recibieron el sustituto.

(4) El autor concluye que " Dolcin " no es un remedio eficaz contra la artritis reumatoide o contra la ósteoartritis y que este producto no tiene ventaja sobre la aspirina sola.

ULNAR DEVIATION OF THE FINGERS

BY

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Ulnar deviation of the fingers at their metacarpophalangeal joints is perhaps the most characteristic deformity of rheumatoid arthritis. Nineteenth-century clinicians, among others Garrod (1859) and Charcot (1881), were impressed by its occurrence in chronic arthritis, but no views on the development of the deformity were recorded. The current opinion, that it results from gravity, is open to objections to be mentioned later. The deformity is unsightly rather than disabling, and may thus be a source of embarrassment to the patient; various splints have been designed for its prevention and correction, but such prophylactic measures do not seem to have been inspired by inquiry into causation.

Features of the Deformity

Study of a number of cases has revealed the following data:

(1) Ulnar deviation may occur in both hands or only one. When unilateral or asymmetrical, the right hand is usually preferred, but by no means always. In right-handed persons the left hand alone may be affected, or the left side may be affected to a greater degree than the right.

(2) All the fingers may be affected; the middle, ring, and little fingers; the ring and little fingers; or the little finger alone.

(3) The deformity may develop at any stage of the disease. The mode of development may be rapid, i.e. within a few months, or so gradual that the patient is unable to date its onset.

(4) Accompanying deformities are common: pronation and flexion of the elbow; flexion or ulnar flexion of the wrist; adduction and opposition of the thumb; and a variety of finger-joint deformities including as a part of the deformity of ulnar deviation, flexion of the metacarpophalangeal joints.

(5) Ulnar deviation of the fingers is not confined causally to rheumatoid arthritis; it may also occur in chronic gouty arthritis, and to a less severe degree in the post-hemiplegic and Parkinsonian hand.

The notable features are then that both or either of the hands may be affected, and all or only some of the fingers; that the deformity occurs in the presence of flexion of the metacarpophalangeal joints; and that it is found in two other unrelated conditions. To account for its origin, all these facts must be satisfied.

Theories of Causation

Two opinions as to the origin of ulnar deviation are current:

(1) that it is an effect of gravity,
(2) that it is produced by muscle imbalance due to severe wasting.

Gravity.—The normal hand, when the arm but not the hand itself is supported, shows ulnar flexion of the wrist because of gravitational pull. It is claimed by supporters of the gravity theory that the fingers of patients with rheumatoid arthritis, whose hands are comparatively immobile for long periods, are thus deflected into ulnar deviation at their metacarpophalangeal joints. That gravity may play some part in the genesis of the deformity is not denied, since in a hand with passively correctable ulnar deviation, the deformity can be minimized by holding the hand in such a position that the effect of gravitational pull is reversed. This does not mean, however, that gravity is necessarily the cause, though it may play a part in maintaining and furthering the deformity.

If gravity were in fact the sole cause of the deformity, one might expect it to be more obvious in the left hand of right-handed patients with arthritis of symmetrical severity, since this hand is less used and, therefore, subject to longer periods of gravitational pull than the right; but this is not found to be so. If it be postulated that use of the hand plus gravity is necessary to produce it, then the reverse would be expected. But, as has been mentioned, in right-handed persons ulnar deviation may affect the fingers of either hand exclusively when the arthritic process is symmetrically severe. It will be mentioned later that patients with ulnar deviation of their fingers show great lateral mobility of their metacarpophalangeal joints, unless the deformity is in an advanced stage and " fixed ". This excessive mobility, not shown by normal fingers when their metacarpophalangeal joints are flexed, is indicative of weakening and stretching of those structures which preserve the limits of motion within the normal range, and sometimes of cartilaginous and bony destruction as well. Gravity in the presence of such abnormal mobility does not, however, necessarily produce the deformity, as patients are seen who have long standing arthritis, abnormally mobile metacarpophalangeal joints, but no ulnar deviation.

Muscle Imbalance.—Muscle wasting is often severe, but a consideration of anatomy makes it difficult to explain ulnar deviation on this basis. The long extensors, and to a lesser extent the long flexors, tend to correct ulnar deviation, as is seen when a patient with the deformity contracts these muscle groups.

There is, however, an exceptional circumstance in connection with the long extensors. If the hands of a number of patients with advanced ulnar deviation of the fingers are examined, some of these will show a displacement of some or all of the extensor tendons, to the ulnar sides of the corresponding knuckles. The affected tendons, instead of crossing the prominences of the knuckles, now lie in the spaces between them, and when they contract their direction of pull is such as to accentuate the deformity. This extensor tendon displacement occurs only with advanced deformity and is evidently the result and not the cause of the ulnar

deviation, since it is absent in the less severe and present in only some of the advanced cases.

There remain the intrinsic muscles of the hand, admittedly often severely wasted, but not in so selective a way that the muscles giving radial movement are weaker than those giving ulnar movement. In this connection, a dynamometer was constructed to measure the power of radial and ulnar movement of each finger, and, though not entirely successful, it indicated that, in patients with ulnar deviation which they could correct voluntarily, the power of radial movement was greater than that of ulnar movement. This might be expected, since the action of the interossei giving radial movement is reinforced by the lumbricals which are radially inserted. These findings did not apply, however, to the little finger of the normal or arthritic hand, at any rate in the extended position where the action of the abductor digiti minimi is more powerful than that of the fourth palmar interosseus.

It seems likely, therefore, that forces other than gravity and muscle imbalance are responsible for the deformity.

The Normal Hand

Inspection of the normal hand shows that flexion of the fingers at their middle and terminal joints by the long flexors is not productive of ulnar inclination.

In many normal hands, if the fingers with their middle and terminal joints extended are flexed at their metacarpophalangeal joints, the degree of flexion being maximal for the little finger and gradually diminishing for the other fingers, then ulnar deflexion occurs (Fig. 1). The ability of normal individuals to produce ulnar deviation of the fingers in this manner varies. Some are able to produce marked ulnar deviation, others scarcely any at all. It will be observed, however, that the deviation is least shown by the little finger, which acts as a bulwark against the other three.

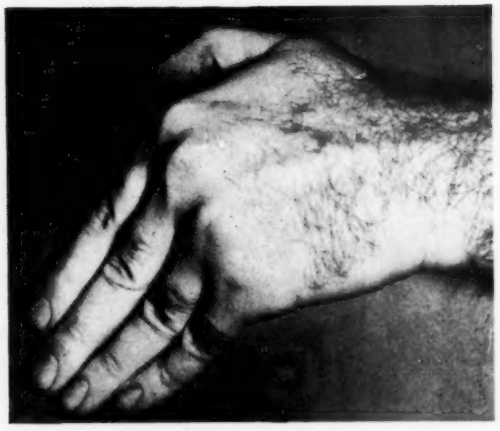

FIG. 1.—Ulnar deviation of fingers of normal hand, metacarpophalangeal joints are flexed with proximal interphalangeal joints extended.

When objects are held or gripped between the fingers and thumb, with the middle and terminal joints extended, the fingers take up the position described above. In the normal use of the hand, this form of grip is only used for certain purposes; more commonly objects are held between the fingers and thumb in such a way that flexion of the middle joints of the fingers is equal to or greater than that of the metacarpophalangeal joints.

The Hand in Rheumatoid Arthritis

During the acute stages of rheumatoid arthritis affecting the hands, the finger joints most obviously affected are the proximal interphalangeal joints. More commonly than not the metacarpophalangeal joints are simultaneously or later affected, but involvement of the middle joints seems more obvious to the patient and to the examiner. The terminal joints are more rarely affected and often escape indefinitely.

The middle joints, being more tightly constructed than the metacarpophalangeal joints, react to inflammation with more pain and stiffness. It will be recalled that these are the joints which enjoy the greatest range of movement during normal use of the hand. In the acute stage, when the patient's fingers are more or less immobilized by pain and stiffness, the thumb lies adducted and the fingers rest in a position of slight flexion of their metacarpophalangeal and proximal interphalangeal joints. Because of this pain and stiffness, the fingers are not much flexed at their proximal interphalangeal joints in grasping movements; they are used together with the thumb rather like a crab's claw. In this way, the proximal interphalangeal joints are splinted in a position close to extension, flexion movements taking place at the metacarpophalangeal joints.

If the arthritic process subsides or remits, flexion of the proximal interphalangeal joints is permitted, and functional use of the hand becomes more normal. More often a subacute stage is reached when pain and stiffness lessen and the patient begins to use his hands more. In many patients the metacarpophalangeal joints are still relatively less painful and stiff than the proximal interphalangeal joints, and the perpetuation of the use of the fingers with partial splinting of the middle joints continues. There is, therefore, a tendency for the metacarpophalangeal joints to adopt a position of flexion of 40 to 75°, and the proximal interphalangeal joints to adopt one of slight flexion or extension.

Although restriction of movement is one result of the rheumatoid process, abnormal mobility is another.

Changes tending to restrict mobility are:

(*a*) swelling of tissues in and around the joint,
(*b*) pannus formation,
(*c*) fibrosis,
(*d*) ankylosis.

Changes giving rise to excessive mobility are:

(*a*) distension of the joint by an effusion with weakening of its capsule,
(*b*) weakening and destruction of ligaments by the inflammatory process.

Cartilaginous and bony resorption have a secondary effect in that they approximate ligamentous and capsular attachments. The balance of these processes is intimately concerned with deformity. If those producing limitation are in the ascendant and a deformity develops it will be within the normal range of joint movement; if, however, those producing abnormal mobility are in the ascendant,

the joint is likely to be deformed in a position outside its normal range, and the deformity, in its early stages at least, will not be fixed. These considerations apply especially to the finger joints. In patients showing ulnar deviation, an abnormal mobility characterizes the metacarpophalangeal joints, which can be moved passively from side to side in the flexed position; such mobility is not found in normal fingers.

Suggested Mode of Development

(1) The tendency of normal fingers to deviate in an ulnar direction when flexed at their metacarpophalangeal joints with the proximal interphalangeal joints extended, and the fact that patients with painful involvement of their proximal interphalangeal joints make grasping movements between the fingers held in this position and the thumb, suggests that the deformity is initiated by this improper use of the hand.

(2) Involvement of the metacarpophalangeal joints by the arthritic process results in greater lateral mobility in the flexed position, and thus allows the deformity to develop.

(3) Involvement of the metacarpophalangeal joint of the little finger results in this finger rolling in an ulnar direction on its metacarpal head when flexed, and it thereby loses its bulwark-like action.

(4) Gravitational pull in an ulnar direction is exerted on the fingers whenever lifting movements between them and the thumb are made in the manner described above, with the hand and the forearm in any position between pronation and supination.

Stages of Deformity

If patients showing ulnar deviation of the fingers are examined, three stages of the deformity are to be found, irrespective of the fingers affected. These are:

(1) voluntarily correctible;
(2) passively correctible;
(3) fixed.

These stages are not necessarily related to the degree or amount of deformity except in a very rough way. The more severe the ulnar deviation the more likely is it to fall into the second or third group, but there is considerable overlap.

First Stage.—At this stage, all or only some of the fingers are affected. The metacarpophalangeal joints of the affected fingers lie at rest in a position of flexion, the proximal interphalangeal joints are extended or moderately flexed and are usually markedly limited in their movements. Mobility of the metacarpophalangeal joints is, however, increased in the lateral plane, and the deformity can be passively accentuated or corrected. Active correction is possible by the patient contracting the appropriate interossei. Extension by the long extensors and flexion by the long flexors also correct the deformity. At rest, however, the affected fingers

fall naturally into ulnar deviation. If at this stage, the arthritic process remits and full normal use of the hand becomes possible, providing the ulnar deviation is not too extreme, it will be evident only when the patient is asked to flex the metacarpophalangeal joints, keeping the proximal interphalangeal joints extended; when, in fact, his fingers adopt the position believed by the author to be responsible for development of the deformity. One sees from time to time patients who have had rheumatoid involvement of the fingers which has to all intents and purposes cleared up, so that the hands appear clinically normal. The fingers of some of these patients when flexed in the described manner, show quite startling degrees of ulnar deviation, which is not evident when the fingers are extended or flexed at all their joints.

Second Stage.—Here the deformity resembles the first stage, except that active correction in the lateral plane is no longer possible by the patient. Extension of the metacarpophalangeal joints is usually limited, so that full correction by the extensors or the long flexors is no longer possible. Passive correction and accentuation are, however, possible, though the former does not extend beyond the mid-line. It is as if the joint had been given a range of movement, maximal in the ulnar direction and minimal in the radial, by compensatory ligamentous relaxation on the radial side and contraction on the ulnar side. Bony destruction, subluxation, and forward dislocation of the proximal phalanges on the metacarpal heads by the pull of the intrinsics are often found. The thumb is usually adducted and partly opposed, and may be semi-ankylosed in this position. The patient can still correct the deformity by pressing against it on some source of resistance when the fingers are at rest, and will be frequently observed to be doing so.

Third Stage.—Here the deformity is fixed, and little or no passive correction is possible.

Distribution of Deformity

Little Finger.—Sometimes the little finger alone is affected. It is not proposed to consider the various deformities to which the little finger is subject, except to note its tendency to roll in an ulnar direction on its metacarpal head, both when its proximal interphalangeal joint is held in extension and when it is ankylosed in partial flexion. Provided the capsule and ligaments of its metacarpophalangeal joint are intact, no great degree of ulnar deviation can occur, but, if these are weakened and easily stretched, increasing ulnar deviation will develop with continued use. This finger is probably pivotal in determining the amount of ulnar deviation of the other fingers, since it acts as a bulwark against the other three if its ligaments are intact. When ulnar deviation of the little finger alone is found, one or more of the following conditions for the development of the deformity of the other fingers is not present,

(1) lateral mobility of the metacarpophalangeal joint;
(2) flexion of the metacarpophalangeal joint;
(3) immobility of the proximal interphalangeal joint.

Ring and Little Fingers.—Ulnar deviation limited to the ring and little fingers

is not uncommon. When this is found, these two fingers are generally more flexed at the metacarpophalangeal joints than the index and middle fingers, which are saved from ulnar deflection by their extended positions.

All Fingers.—Ulnar deviation of all the fingers of a hand is the most common deformity. Flexion of the metacarpophalangeal joints is found, with proximal interphalangeal extension, ankylosis in flexion (functionally similar), or limitation of movement. The fingers lie adducted together in ulnar deviation. The thumb is usually adducted and partially opposed with its terminal joint extended. Inspection of the palm shows a close similarity to the palm of a normal hand when the fingers are flexed in ulnar deviation by the intrinsic muscles.

Unilateral Occurrence and Degree of Deformity.—In otherwise symmetrical cases with ulnar deviation more marked on the right, the greater use of the right hand will explain the deformity. In cases where ulnar deviation is confined to the right hand a similar explanation will hold. The following case is an example of how use of the hand provokes deformity:

M.C., married female, had suffered from rheumatoid arthritis for 7 years. The fingers of both hands were flexed at the metacarpophalangeal joints, the proximal interphalangeal joints being ankylosed in extension. There was marked ulnar deviation of all the fingers of the right hand, those of the left showing very slight ulnar deviation only. She developed a suppurative lesion of the right index finger which necessitated immobilization of the right hand for 3 months. During this time, she perforce used her left hand exclusively. At the end of three months the ulnar deviation of the left hand had increased to such an extent that the deformity was now equal in both hands.

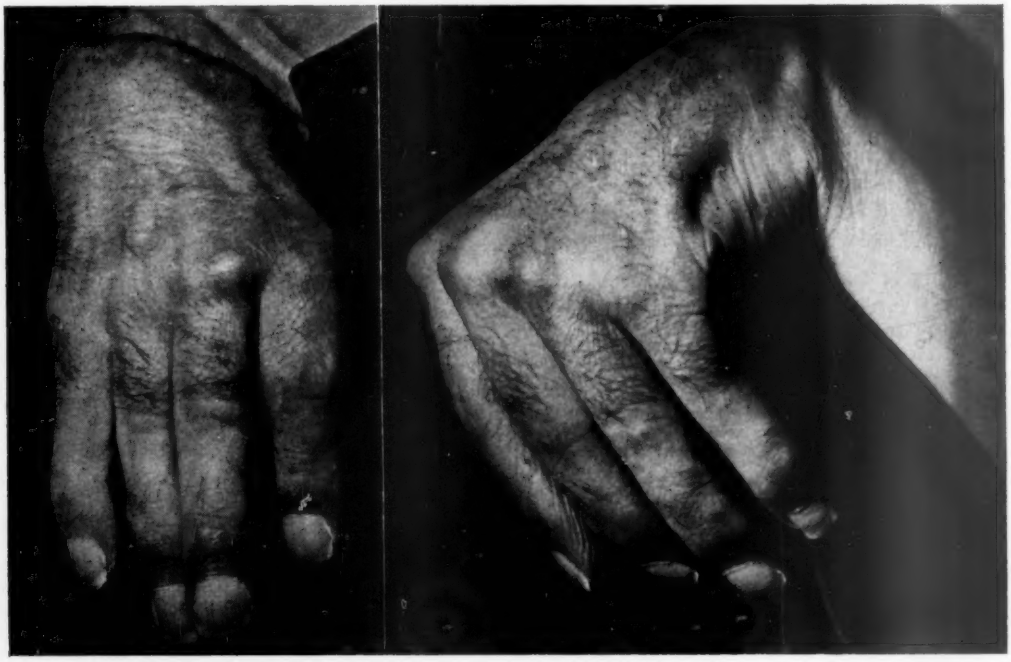

FIG. 2.—Ulnar deviation limited to left hand in right-handed patient. Fingers of right hand ankylosed in extension at metacarpophalangeal joints, and hand functionally useless.

FIG. 3.—Passive accentuation of ulnar deviation of left hand shown in Fig. 2, indicating abnormal lateral mobility of flexed metacarpophalangeal joints.

When ulnar deviation is greater in the left hand or limited to the left in right-handed persons, either the patient has for some reason used the left hand more than the right, or the conditions necessary for development of the deformity are not present in the right hand, either because the arthritic process is asymmetrical or there has been a priority ankylosis of the metacarpophalangeal joints in extension, or the proximal interphalangeal joints are free to flex (Fig. 2). In this patient, ulnar deviation is marked on the left, absent on the right. The right metacarpophalangeal joints are fixed in extension rendering the hand nearly useless functionally, whereas the left metacarpophalangeal joints are in flexion. This patient is in stage two; the deformity can be passively accentuated and largely corrected (Figs 3 and 4*a*, *b*).

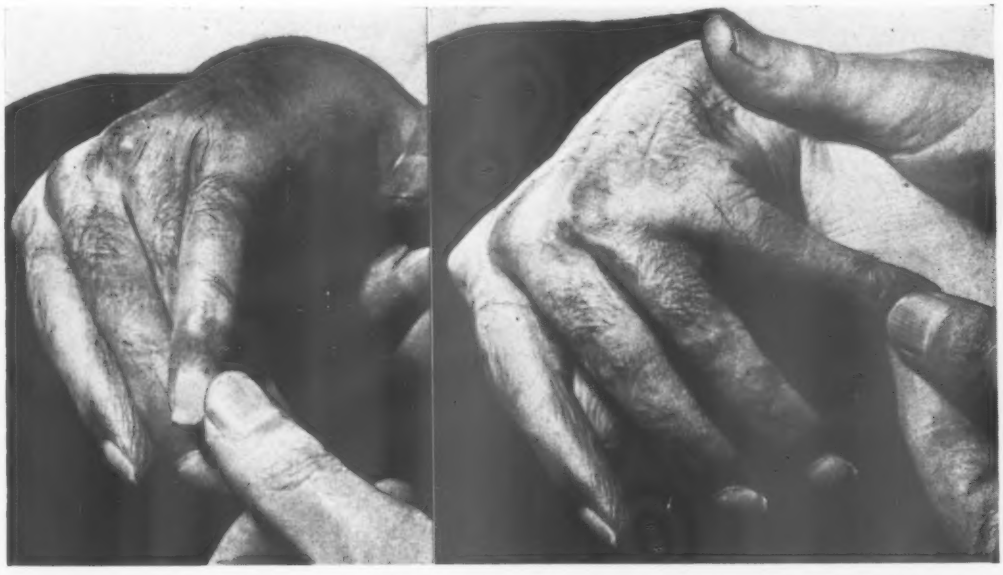

FIG. 4 (*a*).—Passive correction of ulnar deviation of little finger of left hand.

FIG. 4 (*b*).—Marked lateral mobility of little finger of left hand, which cannot act as bulwark.

Although fixation in extension of the fingers of the right hand has occurred, lateral excursion at the metacarpophalangeal joints is not limited (Fig. 5*a*). Attempts to push the fingers into ulnar deviation, however, are held by the bulwark of the little finger (Fig. 5*b*), which shows no abnormal lateral mobility (Fig. 5*c*).

If this patient's fingers were not fixed in extension and he were able to use his right hand as he does his left with flexion at the metacarpophalangeal joints a greater degree of ulnar deviation would be expected on the right than on the left.

FIG. 5 (*a*).—Lateral mobility of ring finger of right hand not limited.

FIG. 5 (*b*).—Attempt to push fingers of right hand into ulnar deviation unsuccessful (see 5*c*).

FIG. 5 (*c*).—Little finger shows no abnormal lateral mobility and acts as bulwark (against 5*b*).

Parkinsonian Hand

The hands of patients with long-standing Parkinson's disease are often found to resemble those of patients with rheumatoid arthritis, insofar as the fingers are flexed at the metacarpophalangeal joints and extended at the proximal interphalangeal and terminal joints (Fig. 6). Such a position would be determined by spasm of the intrinsic muscles. The thumb is similarly adducted and opposed. So far no mention has been made of spasm of muscles as a possible background of deformity of the fingers.

In Fig. 6 the hands of a patient with long-standing Parkinsonism are shown. It will be observed that the fingers of the right hand are in the position described to produce maximal ulnar deflection in the normal hand (that is, flexed at the metacarpophalangeal joints in a plane rising from the radial to the ulnar side of the hand), and that some ulnar deviation opposed by the little finger is present. The fingers of the left hand, however, are less flexed at the metacarpophalangeal joints, lie in the same plane, and show no ulnar deviation. If spasm were productive of ulnar deviation, and this condition affords a perfect example of spasm of equal degree in both hands, the ulnar deviation should be bilateral and symmetrical. That it is not, suggests that active use of the hand produces the deformity, as this patient uses his right hand, but not his left. The immobility of the left hand can be gauged by the position of the markedly adducted and opposed thumb.

(*a*) (*b*)

FIG. 6.—Hands of patient with Parkinsonism. (*a*) Right hand. Flexion of metacarpophalangeal joints. Some ulnar deviation opposed by little finger. (*b*) Left hand. Extension of metacarpophalangeal joints. Hand not used. No ulnar deviation.

Summary

(1) It is suggested that the deformity of ulnar deviation of the fingers is produced by use of the hand in an abnormal manner determined by inability to flex the proximal interphalangeal joints; that the development of the deformity is dependent upon abnormal lateral mobility of the metacarpophalangeal joints

in the flexed position; and that the little finger is pivotal in preventing or allowing the deformity to develop.

(2) The deformity is illustrated in a case of Parkinsonism, and it is claimed that its unilateral nature exempts spasm as a possible cause.

I wish to acknowledge the kind permission of Dr. Milton Rosenbluth, Director, Third Medical Division, Goldwater Memorial Hospital, New York, to study and photograph some of the patients presented in this report.

I also wish to express my thanks to Dr. Arthur Fell for reading the manuscript in its original form and for his criticisms.

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Déviation Cubitale des Doigts

Résumé

(1) La déviation cubitale des doigts serait due à ce que le malade se sert de sa main d'une manière anormale par le fait qu'il ne peut pas fléchir les articulations interphalangiennes proximales, Le dévéloppement de la difformité serait déterminé par la mobilité latérale anormale des articulations métacarpo-phalangiennes en fléxion; le petit doigt servirait de pivot qui empêcherait ou permettrait le dévéloppement de la difformité.

(2) A l'appui de cette théorie l'auteur présente un cas de parkinsonisme où la déviation cubitale n'existe que dans la main droite dont le malade se sert; le spasme musculaire, agissant de deux cotés, ne peut donc pas être mis en cause.

Desviación Cubital de los Dedos

Resumen

(1) La desviación cubital de los dedos se debería a que el enfermo se sirve de su mano de una manera anormal por el hecho de que no puede doblar las articulaciones inter-falangianas proximales. El desarrollo de la deformidad estaría determinado por la movilidad lateral anormal de las articulaciones metacarpo-falangianas en flexión; el dedo meñique actuaría como eje, impidiendo o permitiendo el desarrollo de la diformidad.

(2) Al apoyo de esta teoría el autor presenta un caso de parkinsonismo donde la desviación cubital existe sólo en la mano derecha, usada por el enfermo; el espasmo muscular, presente de ambos lados no puede, pués, causarla.

CONCOMITANT INVOLVEMENT OF THE SHOULDER JOINTS BY PROLIFERATIVE AND DEGENERATIVE ARTHRITIS

BY

ROBERT H. RAMSEY

From the Departments of Surgery and Surgical Pathology (Dr. Lauren V. Ackerman), Washington University School of Medicine, St. Louis, Missouri

This record of an unusual case of arthritis involving both shoulders and both wrists in an elderly female patient emphasizes the difficulty of understanding and classifying the underlying disease process in the chronic arthritides, even when good pathologic material is available for study.

Case Report

Mrs. M.M. (B.H. 175892), a 75-year-old widow of Yugoslavian birth, entered Barnes Hospital on September 7, 1949, with the history of having insidiously developed intermittent pain and stiffness in both shoulders over a ten-year period. These symptoms gradually progressed and about two years before admission, the patient noticed swelling in both shoulders, and pain, swelling, and stiffness in both wrists. From this time on, the pain was moderately severe, almost constant, and aggravated by motion; and the patient became unable to raise either hand up to her hair. Past history revealed that she had been in good general health and had actively done housework all her life.

Physical Examination.—The patient was an alert, asthenic, elderly female in no acute distress and not appearing ill. There was a marked thoracic scoliosis to the right. There was a huge effusion of the right shoulder presenting anteriorly and laterally and a slight effusion of the left shoulder. There was pronounced atrophy of the muscles around both shoulders and both were subluxated upward although they could be passively moved completely around the margin of the glenoid with a coarse grating sensation. All active and passive motion was painful; there was slight peri-articular tenderness. Both wrists showed a prominent effusion with " ballooning " laterally and medially, and in these joints there was slight limitation of motion with pain and slight tenderness. The elbows, hips, knees, and ankles were normal. Heberden's nodes were present. No subcutaneous nodules were found. Head and neck, heart and lungs, abdomen, and neurological examinations were negative. Pelvic examination revealed a lesion on the right labia majora, 1 in. in diameter, which was diagnosed as epidermoid carcinoma.

Laboratory Findings.—Kahn test negative.

Corrected sedimentation rate: 1·3 mm./min. (normal 0·1-0·4 mm./min.).

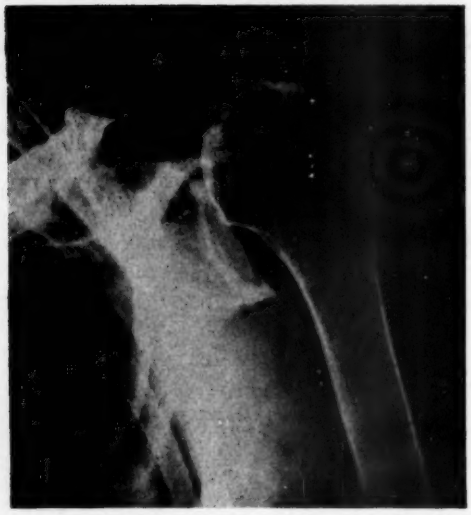
Haemoglobin: 10 g.

Red blood count: 4 million.

White blood count: 8,500 with normal differential count.

Urine analysis: negative.

Culture of joint fluid revealed no growth; the fluid was of clear amber colour and of normal viscosity.



FIGS 1 and 2.—*X* rays of shoulders, showing unusual symmetrical change.

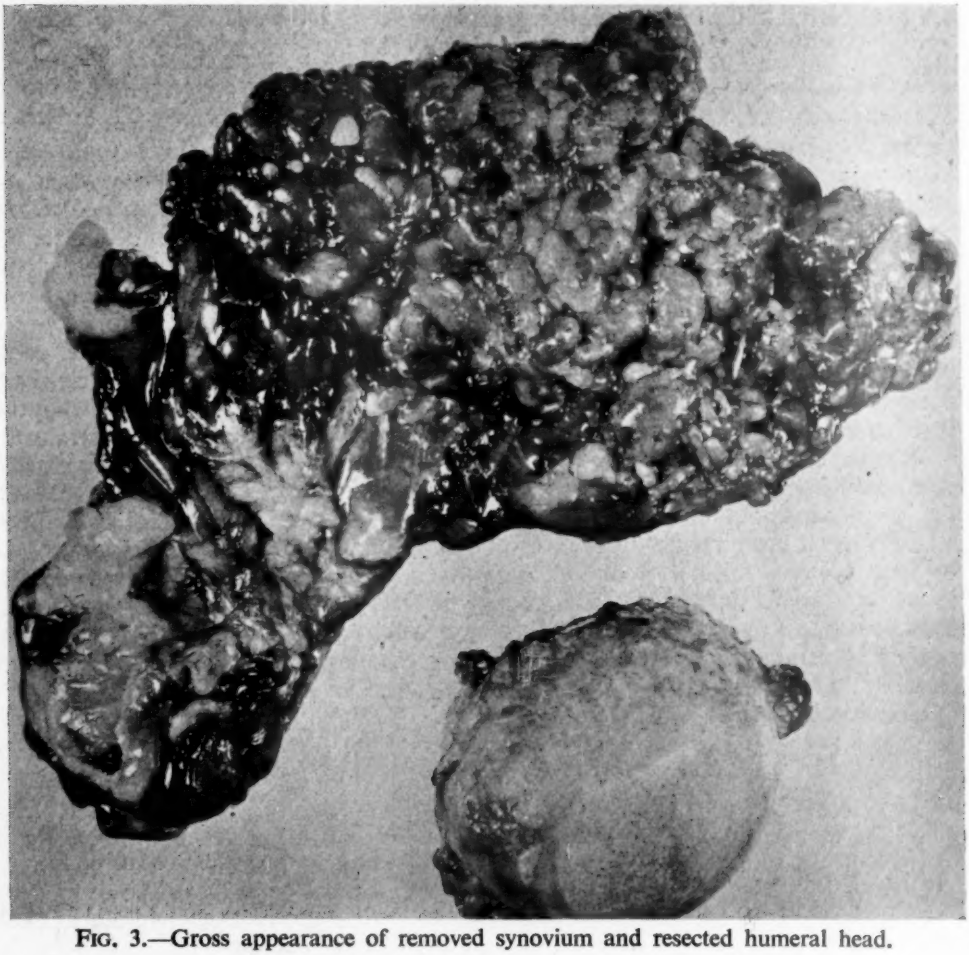


FIG. 3.—Gross appearance of removed synovium and resected humeral head.

Radiological Examination.—*X* rays of the shoulders (Figs 1 and 2) revealed an upward subluxation, decrease in width of joint space, irregular demineralization of the bones of the shoulder girdle, slight marginal spurring of the humeral head and glenoid, and subchondral condensation of the humeral head, the latter being particularly marked on the right side. *X* rays of the wrists showed soft tissue swelling, irregular demineralization of the distal radius, the ulna, and all of the carpals, and marked narrowing of the radial-carpal articulations.

Operation.—On September 8, 1949, the right shoulder was explored by an anterior approach. When the joint was entered an estimated 250 ml. clear amber-coloured synovial fluid escaped. The entire anterior and lateral synovium was removed, and the upper end of the humerus was resected just distal to the articular margin (Figs 3 and 4).

A two-month follow-up revealed no recurrence of the effusion, but only a few degrees of active motion were possible because of the painful grating produced by attempted motion. The wrists and left shoulder were essentially unchanged. The epidermoid carcinoma of the vulva was treated by the Department of Obstetrics and Gynaecology shortly after the operation on the shoulder.

Pathology

Gross.—The synovial specimen (Fig. 3) measured 18×8 cm. in area and was 1 to 2 cm. thick. The bulk of the tissue was hypertrophied synovium with a layer of loose fibrous tissue 1-2 mm. thick representing part of the underlying capsule. The synovial surface was composed of closely packed nodules and papillary masses of hypertrophied synovium and was of reddish-grey colour. Some of the nodules were as much as 1 cm. in diameter. A few of the villi were yellowish-white and had the consistency of fat. The humeral head (Fig. 4) was seen to be devoid of cartilage

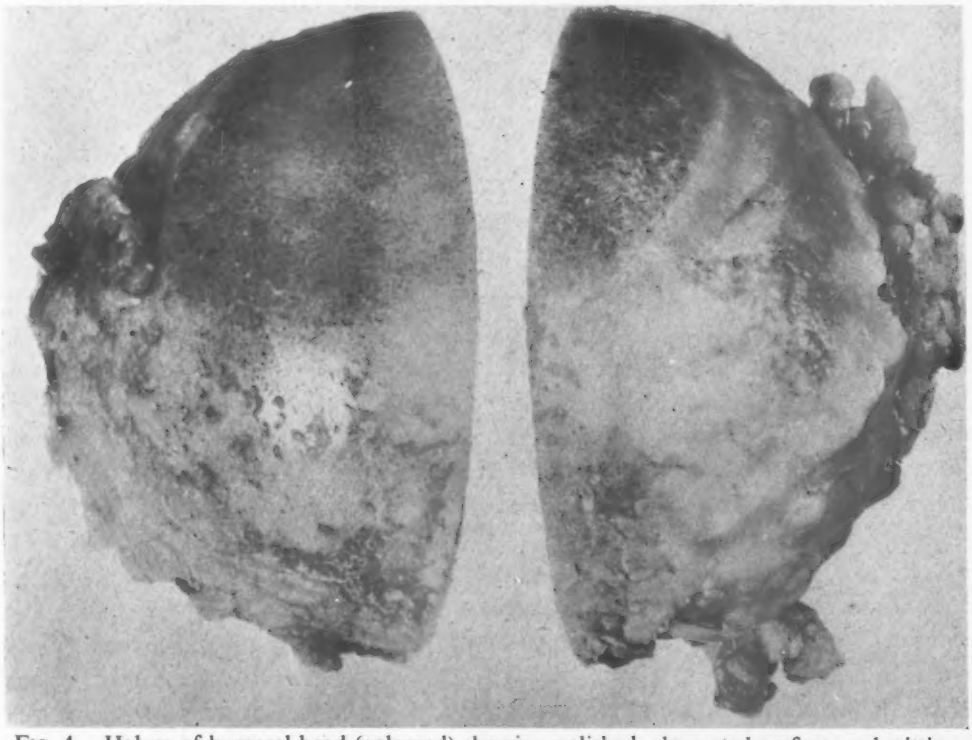


FIG. 4.—Halves of humeral head (enlarged) showing polished, eburnated surface and pitting.

except near the articular margin, and most of the surface was a highly polished, eburnated bone covered with fine, shallow, punctate pits. Near the articular margin a portion of the articular surface was covered by a thin layer of white, fairly dense, fibrous tissue, and a few irregular overgrowths of a dull hyaline cartilage were present.

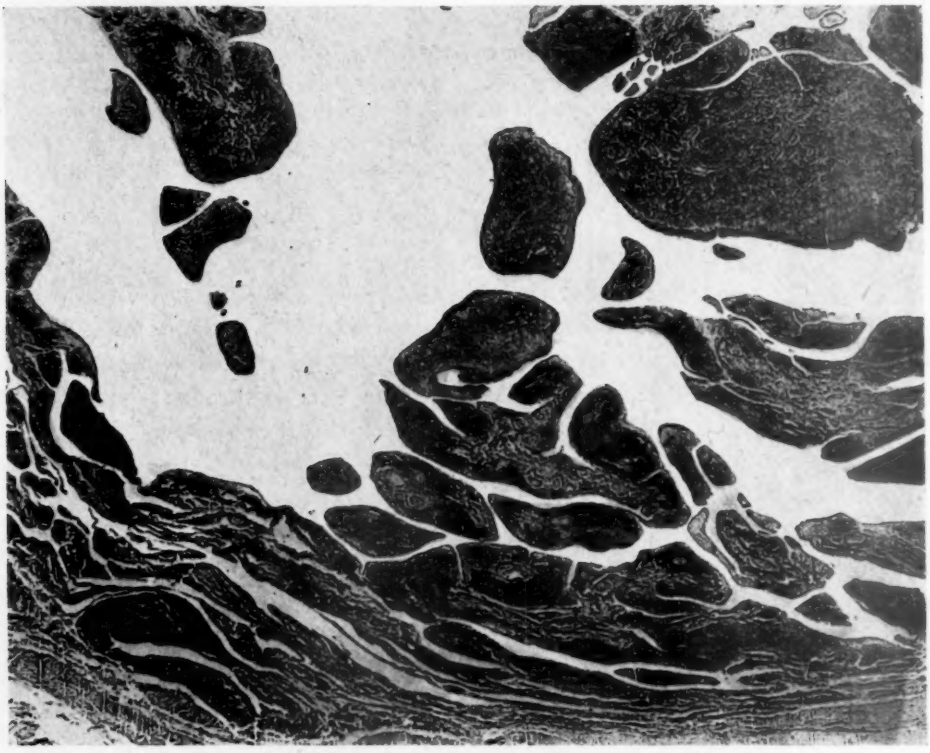


FIG. 5.—Low-power photomicrograph of synovium.

Microscopic.—The synovium (Figs 5 and 6) showed a villous type of hypertrophy; the surface layer was 3 to 5 cells thick, and was made up of cuboidal, ovoid, and flat cells 10-12 microns in diameter. The stroma of these villi was composed of a vascular fibrous connective tissue with a relatively small amount of collagenous intercellular substance, and showed slight oedema. The dominant features were the diffuse plasma-cell infiltration and the multiple focal collections of both plasma cells and lymphocytes. In these collections the plasma cells were usually more numerous than the lymphocytes. A few polymorphonuclear leucocytes were seen.

Section of the humerus (Fig. 7) showed an articulating surface of compact bone which immediately below the surface became trabecular in structure; the deeper trabeculae were thin and somewhat sparse. Many of the lacunae close to the articulating surface were empty. The intertrabecular connective tissue just below the surface was a loose cellular fibrous tissue with moderate plasma-cell and lymphocytic infiltration; deeper it was adult adipose tissue with many small

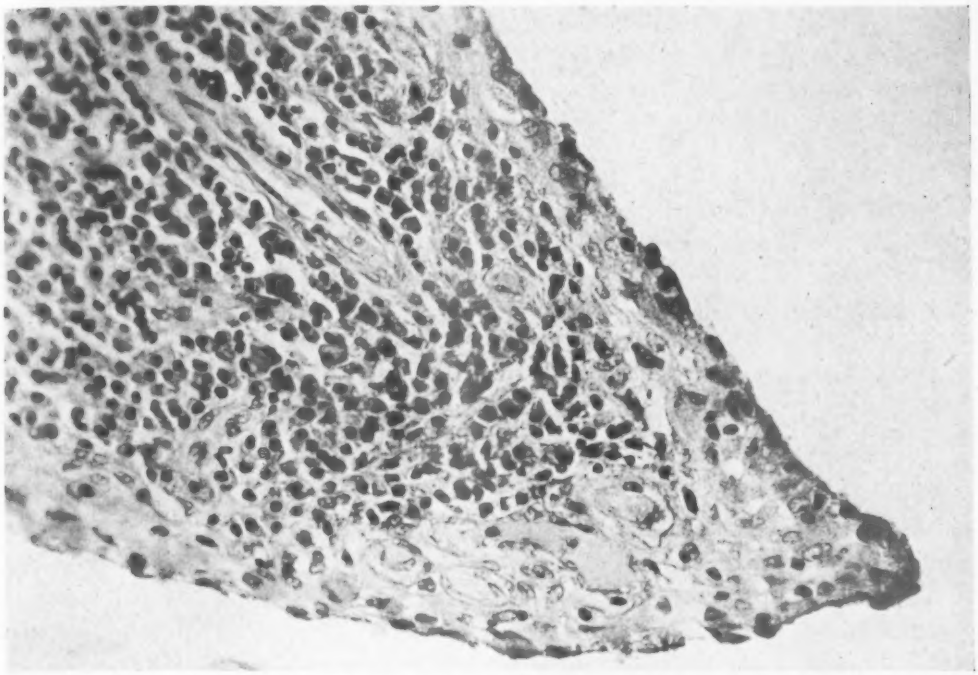


FIG. 6.—Photomicrograph (×400) of synovial villus, showing hyperplasia of the living cells and stroma, and prominent plasma-cell infiltration.

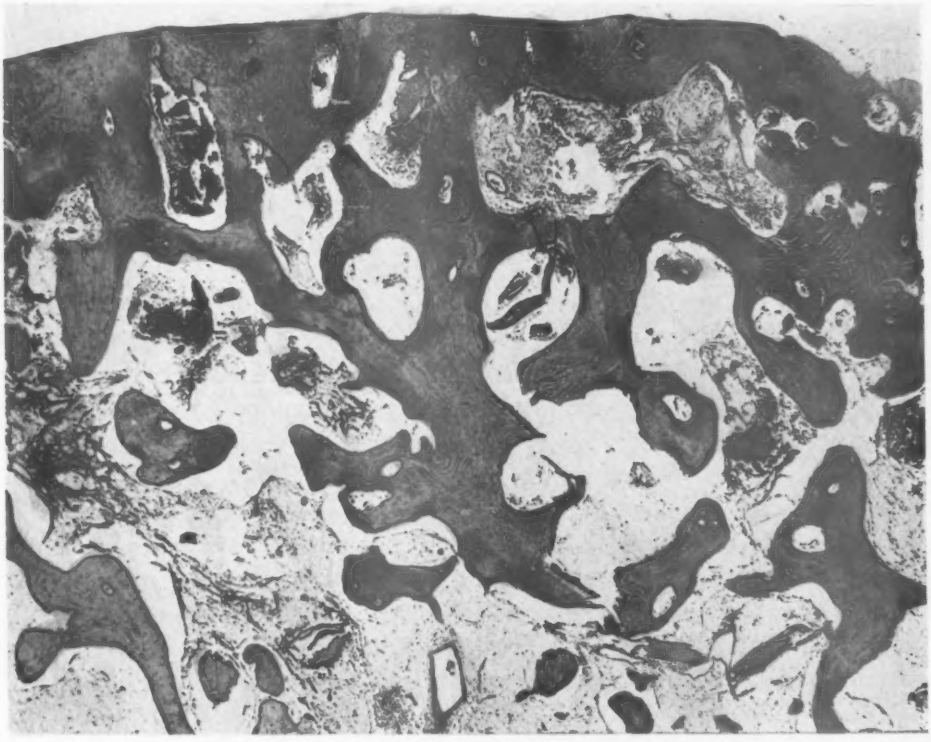


FIG. 7.—Photomicrograph (×225 of humeral head, showing articulating bony surface at the top.

fibrous strands and no inflammatory elements. Near the articular margin the surface of the bone was covered with a thin layer of cellular fibrous tissue with the cells and collagen fibres arranged parallel to the surface.

Discussion

From the pathological standpoint it is immediately apparent that at least part of the change in this shoulder joint represented a severe form of degenerative or osteo-arthritis. The loss of the cartilage surface with the formation of a polished, eburnated bone surface, the marginal lipping, and the subluxation are typical features that have been described by virtually all published studies of this condition. However, as Keefer (1935) points out:

> in spite of the fact that pain in the shoulder is extremely common, it is not due to osteo-arthritis very often;

it would therefore be most unusual to see a severely symptomatic degenerative arthritis involving both shoulders and both wrists in a patient without any symptomatic joint disease in the weight-bearing joints unless there was some concomitant disease process in these symptom-producing joints.

In addition, this case shows evidence of rheumatoid arthritis in the pronounced synovial proliferation with round-cell infiltration, as well as in the mild connective-tissue proliferation with inflammatory changes in the marrow spaces just below the articular surface. If it is true, as claimed by Allison and Ghormley (1930) and by Rosenberg (1949), that the non-perivascular collections of round cells to form follicles are pathognomonic of rheumatoid arthritis, then this case must fall into that category. It is the author's feeling, however, that these follicle-like collections are non-specific. The distribution of joint disease in this case is also suggestive of rheumatoid arthritis.

Nichols and Richardson (1909), in their comprehensive study of the pathology of what they termed " proliferative " and " degenerative " arthritis, describe a marked proliferation of the synovium that sometimes occurs in the latter type and may result in the formation of papillary masses; this they termed " fungoid joint ". However, they were grouping under the term " degenerative arthritis " such conditions as Charcot's joints, traumatic arthritis, osteochondromatosis, and gout. As later studies appeared and degenerative arthritis became more exactly defined the synovial change became a less prominent feature. Thus, Ely (1914) notes focal round-cell infiltration but no real proliferation of the synovium; Allison and Ghormley (1930) state that the portion of the synovium near the articular margin may become villous, show hyperplasia, and have occasional areas of small-cell infiltration; and Abrams (1949) mentions only that " the synovial membrane frequently is normal but may show an increase in number and size of villi ". So it seems that judged by the more recent concepts of the pathology of arthritis the synovial proliferation in this case cannot be considered to be the result of degenerative arthritis alone.

This case was reviewed by Dr. Granville Bennett (1950), who considered it

to represent the simultaneous occurrence of rheumatoid and degenerative arthritis in the same joints. Dr. J. Albert Key (1950) did not think the proliferative component of this case could be classified as rheumatoid arthritis. Our search of the literature revealed no similar change of such a severe nature in the shoulder joint.

Summary

An unusual case of severe chronic arthritis involving both shoulders and wrists in a 75-year-old female is reported, with a pathological study of the surgically removed synovial membrane and humeral head. The clinical, radiographical, and pathological findings lead to the conclusion that this condition may represent the concomitant occurrence of proliferative and degenerative arthritis.

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Atteinte Concomitante des Articulations de l'Épaule par l'Arthrite Proliférative et Dégénérative

Résumé

On rapporte un cas rare d'arthrite chronique grave atteignant les articulations de l'épaule et du poignet chez une femme de 75 ans. L'examen anatomo-pathologique des membranes synoviales prélevées chirurgicalement et l'étude clinique et radiologique de la malade mènent à la conclusion qu'il pourrait s'agir d'une arthrite proliférative et dégénérative survenant en même temps.

Implicación Concomitante de las Articulaciones del Hombro por Artritis Proliferativa y Degenerativa

Resumen

Se relata un caso raro de artritis crónica grave afectando las articulaciones del hombro y de la muñeca en una mujer de 75 años. La investigación anatomo-patológica de las membranas sinoviales extraidas quirúrgicamente y el estudio clínico y radiográfico de la enferma llevan a la conclusión de que se pueda tratar de una artritis proliferativa y degenerativa concomitante.

TREATMENT OF DYSREACTION DISEASES WITH NITROGEN MUSTARDS*

BY

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The Dysreaction Diseases

It is many years since we first began (Jiménez Díaz, 1920) the clinical study of certain diseases for which the name allergic has since been generally accepted. We studied the sensitizing factors in Spain and demonstrated sensitization to various substances, some reported beforehand and others discovered in the course of our studies.

Treatment of Asthma.—Many cases of bronchial asthma, which resisted every allaying measure, improved and apparently recovered or remained free from attack. As time went by we centred our attention more and more on the failures. Hurst (1943) commented humorously that he, himself an asthmatic patient, had seen that all the methods commended for the treatment of asthma were successful in 80 per cent. of cases and that this percentage is the same for iodides, desensitization, and allergen-free chambers. No doubt the rates of failure are greater than those generously admitted by Hurst, and are matter for serious thought. If the asthmatic patients are isolated from the allergens deemed harmful, why do the crises recur as if new sensitization had supervened ? and why is it that, if certain disregarded reacting factors change, these allergens are no longer harmful ? One of the most noteworthy examples is high fever, which overcomes the asthmatic status even in patients in an allergenic environment, e.g. a patient sensitized to fungi, a condition still persisting at his home by the sea. This observation worried us, and we studied its possible mechanism hoping to find a common factor which would have more certain and protracted results. We were able to show that artificially-induced fevers inhibited anaphylactic shock (Arjona and others, 1944), but the reason escaped us. We then thought that certain enzymes might be inactivated at a high temperature, and considered the fact that the activity of cholinesterase is attenuated over 38° C. We studied the plasma and urine of patients with allergic diseases and demonstrated the excretion of a stable acetylcholine ester in the urine during crises of migraine (Jiménez Díaz and others, 1941; Lorente and Jiménez Díaz, 1943). At that time acetylase was unknown and it was believed that cholinesterase had a double effect (the formation and destruction of acetylcholine) so that in our case we thought perhaps this " cholinergic paroxysm " (the attack of migraine) resulted from the excessive production of these esters, which would be suppressed when they were inactivated by the raised temperature. However, we were unable to demonstrate an over-production of such substances in attacks of bronchial asthma.

Nucleus of Dysreaction.—It is evident, nevertheless, that different circumstances can mitigate or even abolish the attacks in asthmatic patients. We pointed out (Arjona and others, 1944) the " reversible nature " of asthmatic conditions even in cases in which, on account of its unremitting quality and secondary effects, an organic change seemed

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obvious. We reported cases in which asthma disappeared because of jaundice, myxoedema, or the onset of nephritis, and still seeking a common factor, suggested that it might be ascribed to the cholesterol in plasma. This idea seemed strengthened by the concurrent demonstration of low blood cholesterol figures in the majority of cases of unremitting infectious asthma. Treatment with injections of cholesterol gave no results, even if the blood cholesterol did not in fact rise, and transfusion of jaundice plasma was not effective in asthma. Hence the problem remained unsolved, but it was evident (Jiménez Díaz, 1944) that sensitizations, besides pollinosis, have an adjunctive value in bronchial asthma. The main point of so-called allergic diseases is the " nucleus of dysreaction ". Only when this is known and may be subjected to modification, we said, will it be possible to overcome asthma whether sensitizing agents are present or not.

Reversibility of Rheumatoid Arthritis.—Parallel to these observations on asthma are those of Hench (1949) on the " potential reversibility of rheumatoid arthritis ", another disease whose aetiology remains obscure, but in the genesis of which the role played by the " hyperergic reaction " is quite obvious. Hench pointed the effects of pregnancy, jaundice, etc., and his discovery (Hench and others, 1949) gave the means of modifying certain diseases by changing the " reaction ". The effects of compound E and ACTH do not depend upon the existence of primary dysfunction of the adrenals and pituitary gland, or upon an excessive consumption of these hormones in such patients, but could be explained by the change which they bring about in the organic reaction against sundry stimuli. The discovery of Hench and his colleagues was made at a time when new discoveries in the field of pathology have strengthened the idea of a common dysreactional ground in diseases aetiologically and pathologically different.

Diseases of Adaptation against Stress.—The studies of Selye (1950a, b) on the " diseases of adaptation against stress " suggest the varying consequence of stress through the reaction of the peripheral-hypothalamus-pituitary-adrenal system. Stress provokes the production of ACTH and hormone X in the anterior lobe of the pituitary gland, and inhibits the production of other less essential hormones (gonado-somato- and thyrotrophic) in organic defence. ACTH arouses the production of glucocorticoids, which stimulate gluconeogenesis, lympholysis, and reticulo-endothelial reaction, and inhibit the histaminergic reaction and fibrosis; the X hormone promotes the formation of mineralcorticoids which act antagonistically, furthering fibrinoid degeneration, hyalinosis, and the formation of granulomata. This is not the proper time for a critical evaluation of Selye's thesis, which may not be admissible in its entirety but has undoubtedly underlined the role of stress and endocrine reaction in the genesis of a large group of diseases.

Collagen Diseases.—The studies of Klinge (1933), Vaubel (1932), and Rich and Gregory (1943a, b) have shown how to obtain lesions by injecting heterologous proteins which characterize various diseases, such as rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa, scleroderma, dermatomyositis, and Buerger's disease. The concept of " collagen diseases " having been established by Klemperer and others (1941), all these processes would fall within these conditions; although it should be noted that the alterations of collagen are not always due to an allergic mechanism and that the lesions are not always equivalent. Thus from different starting points a common nucleus of dysreaction has been reached and accepted in this group of diseases in which a " potential reversibility " exists.

Effects of Cortisone and ACTH and of the Nitrogen Mustards

The mechanism whereby cortisone and ACTH modify this common dysreactional factor is little understood at present. It seems likely, however, that its action must in part be connected with changes in antibody formation. Collagen disease in conditions arising from sensitization to foreign proteins might

be explained by local precipitation on the tissue of the antigen-antibody complex (Altshuler and Angevine, 1949; Schwab and others, 1950). We have shown the direct precipitation of albumins in the kidney in nephritis by nephrotoxic serum (Roda and others, 1949); and Heymann and others (1950) showed a local deposit of labelled antibody in damaged tissue.

Dougherty and White (1943) demonstrated an increase of phagocytosis, gamma-globulin, and antibodies by adrenal and pituitary hormones, possibly connected with lympholysis. Other authors have not confirmed the stimulation of antibodies by ACTH (Eisen and others, 1947; Herbert and de Vries, 1949), but lympholysis is constantly found (Hills and others, 1948; Thorn and others, 1948, 1950). Moreover, the role of the lymphocytes in antibody formation has been stressed by many authors (Sabin, 1939; McMaster and Hudack, 1935; Dougherty and others, 1945). On the other hand, Green (1950) has connected the therapeutic effect of ACTH with its antimitotic action.

Owing to the difficulties of obtaining sufficient amounts of ACTH and cortisone, we began to experiment with nitrogen mustards in the treatment of these allergic diseases for the following reasons:

(1) They produce leucopenia and lympholysis (Pappenheimer and Vance, 1920; Gilman and Philips, 1946).

(2) They have an antimitotic effect.

(3) There is a similarity, though not identity (since they can be produced even when the adrenals are absent), between the action of nitrogen mustards and the " reaction of alarm " (Karnofsky and others, 1948).

(4) They cause adrenal hyperplasia and increased rate of excretion of 17-ketosteroids (Betz and others, 1949; Heusghem and Charlier, 1949).

Present Investigations

In a series of studies on the action of nitrogen mustards we noted that the injection of nitrogen mustards produces an increased excretion of 17-ketosteroids, clearly perceptible hyperplasis of the adrenals, and a checking effect of anaphylactic shock in the sensitized guinea-pig, preventing bronchial asthma experimentally induced by spraying the antigen in a chamber in which the sensitized guinea-pig is kept. These facts coincide with the observations of other authors (Table I). Other instructive facts also came to light, and many phenomena of experimental hypersensitivity were checked by ACTH, cortisone, and nitrogen mustards. Hence the vascular and cardiac valvular lesions induced by injections of heterologous sera and inhibited by ACTH (Seifter and others, 1950) are also inhibited by nitrogen mustards (Dammin and Bukantz, 1949; Forman and others, 1949). Schwab and others (1950) also observed this inhibition and the concurrent suppression of the adsorption of the complement. The phenomenon of Shwartzman is inhibited by ACTH (Soffer and others, 1950), and also by nitrogen mustards (Schlang, 1950). The phenomenon of Arthus, inhibited by cortisone and ACTH (Germuth and Ottinger, 1950), is likewise inhibited by nitrogen mustards (Forman and others, 1949; Dammin and Bukantz, 1949). Formalin-induced arthritis, inhibited by

TABLE I

PARALLELISM BETWEEN ACTION OF ACTH AND CORTISONE AND OF NITROGEN MUSTARDS

Process		ACTH and Cortisone		Nitrogen Mustards	
		Effect	Author and Date	Effect	Author and Date
Lympholisis		increase	Hills and others, 1948 Thorn and others, 1948, 1950	increase	Gilman and Philips, 1946
Adrenal Glands		hyperplasia	—	hyperplasia	Karnofsky and others, 1948 Betz and others, 1949 Heusghem and Charlier, 1949
Mitosis		antimitosis	Green, 1950	antimitosis	—
17-ketosteroid Excretion		increase	Thorn and others, 1948, 1950	increase	Betz and others, 1949 Heusghem and Charlier, 1949 Jiménez Díaz, 1950 Jiménez Díaz and others, 1950a, b
Experimental Allergic Phenomena	Formalin-induced arthritis	inhibition	Selye, 1949, 1950a, b	inhibition	Meier, 1950
	Arthus' phenomenon		Germuth and Ottinger, 1950		Dammin and Bukantz, 1949 Forman and others, 1949
	Shwartzman's phenomenon		Soffer and others, 1950		Schlang, 1950
	Arteritis and valvular lesions induced by homologous sera.		Seifter and others, 1950		Dammin and Bukantz, 1949 Forman and others, 1949
	Experimental anaphylactic asthma		—		Jiménez Díaz and others, 1950a, b, c

ACTH (Selye, 1949, 1950a, b), is also checked by nitrogen mustards (Meier, 1950). We have seen the checking effect of these substances on anaphylactic shock and, furthermore, on experimental asthma induced in sensitized guinea-pigs. Robson and Duthie (1950) demonstrated a similarity between the action of ACTH and that of nitrogen mustard on the capillary permeability.

Although differences do exist, it is obvious that the effects of nitrogen mustards, ACTH, and cortisone have many points of contact, and that their action is similar as regards the phenomena of shock and immunity. Nitrogen mustard (NH3)

stimulates adrenal function, but its effect is due not only to this factor, but also to its direct action on antibody formation and antigen-antibody combination, and its precipitation on collagen substances.

Technique.—At first we used the doses applied in Hodgkin's disease, but in some cases leukopenia was too pronounced and symptoms of thrombocytopenic purpura occurred. It was deemed advisable to decrease the dosage and at present we give three or four injections at the most, of 4 to 6 mg. each, according to the weight of the body. Injections are given on alternate days by the usual technique for intravenous serum injections. We are at present trying another technique involving smaller doses over a longer period. It is obvious that with time this therapy may be improved, and certain allied compounds (such as naphtilic) may be used by the oral route. Moreover, by changing the chemical structure, more active and less toxic compounds might be found.

Results.—Rheumatoid arthritis, asthma, psoriasis, scleroderma, periarteritis nodosa, Buerger's thrombo-angiitis, and iritis were treated with nitrogen mustard (tri-B-chloroethylamine) with the following results.

(1) *Rheumatoid Arthritis.*—Up to the present 32 cases have been treated (Jiménez Díaz, 1950; Jiménez Díaz and others, 1950a, b, c). The most regular effect was that on pain which, in every case, improved, and in the majority disappeared entirely. At the same time, the inflammation of the joint and the effusion underwent a striking decrease, which could be shown objectively by direct measurement. This permitted a greater degree of movement; contractions, and particular positions taken to mitigate pain, disappeared. Bed-ridden patients began to move, walk, and use their hands, and in the best cases a striking return to normal occurred. The majority of patients treated were cripples of 5 to 10 years standing, and the improvement was startling. True ankylosis, understandably, was not influenced, but the outstanding part played by the pain, inflammation, and contractions in joint immobilization was clearly seen, and some of the more acute cases without ankylosis made a full recovery. The results (classified in Table II) were as follows:

(*i*) pronounced leukopenia and lymphopenia were present in the blood;
(*ii*) the figure for eosinophils fell;
(*iii*) in contrast with what has been observed with ACTH and cortisone, the sedimentation rate changed very little, if at all (occasionally it increased temporarily, and it decreased slightly in a few cases);
(*iv*) where fever existed it disappeared;
(*v*) the excretion of 17-ketosteroids steadily mounted;
(*vi*) the excretion of uric acid fell at first and rose again afterwards.

(2) *Bronchial Asthma.*—We have already published our first results in this disease (Arjona and others, 1944). Thirteen cases have been treated up to date (Table III), mostly ones of long standing that had not improved with standard treatments and had been in our department of allergy for a long time. The first case involved a woman who had had protracted attacks for many months and derived only brief respite from aminophyllin and adrenaline. From the first injection she was able to lie down and rest; the condition disappeared after the second injection, and she has remained thus for six months. In promising cases, dyspnoea

TABLE II

RESULTS OF TREATMENT WITH NITROGEN MUSTARDS IN 32 CASES OF RHEUMATOID ARTHRITIS

Patient	Sex	Result	Patient	Sex	Result
M.M.	F	+++	J.H.	F	+++
C.S.	F	+++	M.I.	M	+++
P.G.	F	+++	J.C.	F	+++
B.S.	M	+	J.H.	M	+
M.R.	M	+++	C.M.	F	++
F.G.	F	+	E.C.	M	++
F.S.	M	+++	M.C.	F	++
J.M.	M	+++	M.A.	F	+++
E.S.	M	+	E.B.	F	+++
M.B.	F	+++	S.H.	M	+++
L.E.	F	++	M.J.	F	+
D.F.	F	+++	S.M.	F	++
A.N.	F	+++	M.P.	F	++
M.L.	M	++	B.B.	F	+++
J.G.	M	++	I.S.	F	+
J.P.	M	+++	A.F.	M	+++

Eighteen (56·25 per cent.) +++ Very Good (disappearance of pain, swelling, etc., and recovery of movement, excepting joints with osseous ankylosis).
Eight (25 per cent.) ++ Good (accentuated decrease of subjective phenomena with evident improvement in movement).
Six (18·75 per cent.) + Poor (little improvement; decrease of pain).

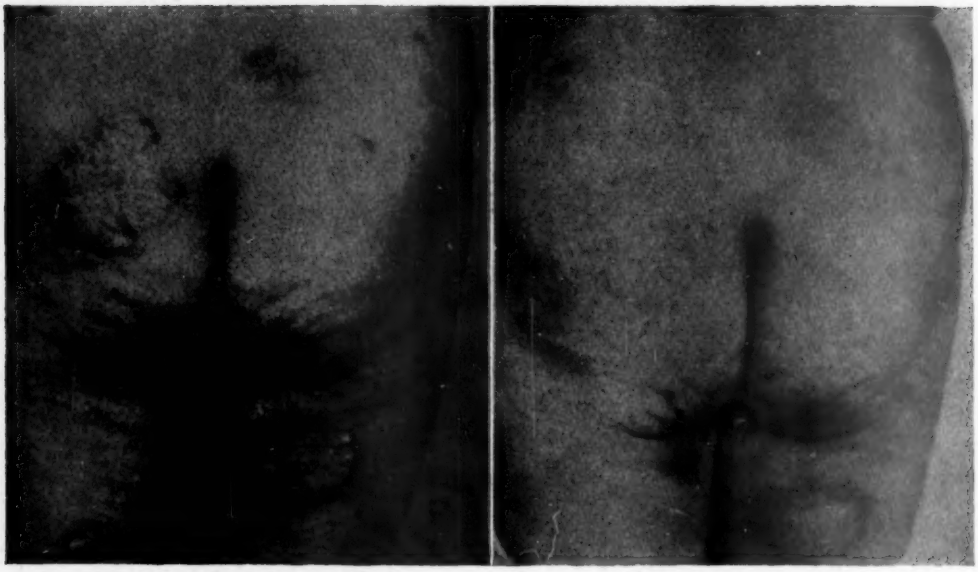
TABLE III

RESULTS OF TREATMENT WITH NITROGEN MUSTARDS IN 13 CASES OF SEVERE INFECTIOUS ASTHMA

Patient	Sex	Result	Relapse
V.I.	M	+++	no
A.P.	F	+++	no
M.G.	F	+++	no
J.G.	M	+++	no
F.C.	M	+++	no
M.A.	M	+	—
R.R.	F	++	yes
S.H.	M	+++	no
M.T.	F	+++	no
A.S.	F	+++	no
M.A.	F	+++	yes
F.M.	F	+++	no
P.N.	M	+	—

+++ freed from asthmatic symptoms, ten (76·9 per cent.).
++ greatly improved, one (7·7 per cent.).
+ no improvement, two (15·4 per cent.).

disappeared after the second injection and, concurrently, objective improvement in auscultation was noticeable together with an improvement of the vital capacity as shown by the spirographic curves. The effect was parallel to the fall in eosinophils per c.mm. The results in asthma were more striking than those observed in rheumatoid arthritis.



(*a*) before treatment (*b*) after treatment

FIGURE.—Effect of nitrogen-mustard therapy in a case of psoriasis.

(3) *Psoriasis.*—One of our rheumatic patients had large patches of psoriasis. The effect of treatment is shown in the Figure. Orbaneja (1951) has since treated many cases; cutaneous symptoms have disappeared in every instance and, though a relapse occurred in some within a few weeks, in others the improvement has been maintained for 8 months.

(4) *Other Conditions.*—We treated one female patient with scleroderma and distal arthritis. The hard oedema was reduced, the skin became flexible, and pain was relieved.

Of three cases of thrombo-angiitis, two with persistent phlebitic nodules got rid of them, and the circulation improved in all three.

In one case of severe iritis, the patient had already lost one eye and sight was minimal in the other, with marked pain. When she was treated by my assistant, Dr. Roda, sight became normal in the remaining eye, so that she could read and work under normal conditions, and pain disappeared after the second injection.

Summary

(1) The author's studies of the reversibility of bronchial asthma by modification of the " nucleus of dysreaction " were in some ways parallel to Hench's observations on the " potential reversibility of rheumatoid arthritis ", another disease in which an important role is played by " hyperergic reaction ".

(2) Experiments with the treatment of various allergic diseases with nitrogen mustards were tried, because nitrogen mustard (NH3) had been shown to produce a range of effects somewhat similar to those produced by ACTH and cortisone, and to have a similar action as regards the phenomena of shock and immunity.

(3) In the majority of 32 cases of rheumatoid arthritis and 13 cases of asthma, considerable improvement occurred. Other conditions which benefited from the treatment were psoriasis, scleroderma, thrombo-angiitis, and iritis.

(4) The author thinks that these first results may open a promising new line of future research.

This work was carried out with the help of Drs. López García, Merchante, and Perianes, on the clinical side; and Drs. Arjona, Aguirre, Perianes, Linazasoro, and Vivanco, on the biochemical and experimental side.

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Traitement des " Maladies de Dysréaction " par la Moutarde Azotée

RÉSUMÉ

(1) Les études de l'auteur sur la reversibilité de l'asthme bronchique par la modification du " noyau de dysréaction " ont été parallèles aux observations de Hench sur la " reversibilité potentielle de l'arthrite rhumatismale ", une autre maladie dans laquelle la réaction hyperergique joue un rôle important.

(2) En partant de la similarité de certains effets des moutardes azotées, de l'ACTH et de la cortisone, ainsi que de la similarité d'action de ces substances dans les phénomènes de choc et d'immunité, on a traité, à titre expérimental, plusieurs maladies allergiques par des moutardes azotées.

(3) Dans la plupart des 32 cas d'arthrite rhumatismale et dans 13 cas d'asthme on a obtenu une amélioration considérable. Des résultats favorables de ce traitement on été observés également dans le psoriasis, la sclérodermie, la thrombo-angéite et dans l'irite.

(4) L'auteur considère que ces premiers résultats ne sont qu'un encouragement aux recherches ultérieures.

Tratamiento de " Enfermedades de Disreacción " con Mostaza Nitrogenada

RESUMEN

(1) Los estudios del autor acerca de la reversibilidad del asma bronquial por modificación del núcleo de disreacción han sido paralelos a las observaciones de Hench sobre la reversibilidad potencial de la artritis reumatoide, otra enfermedad en la que la reacción hiperérgica juega un importante papel.

(2) Se ha realizado experiencia sobre el tratamiento de algunas enfermedades alérgicas con mostaza nitrogenada, partiendo de la similaridad entre muchos de los efectos de esta droga con los de la ACTH y la cortisona, principalmente en relación con los fenómenos de choque e inmunidad.

(3) Se han obtenido mejorías, cuya frecuencia se menciona en el texto, en algunas ocasiones impresionantes, en 32 casos de artritis reumatoide y 13 casos de asma. También se han visto beneficios en casos de esclerodermia, trombo-angitis, iritis y psoriasis.

(4) El autor considera que estos primeros resultados constituyen solamente un horizonte prometedor para el futuro.

TOTAL AND DIFFERENTIAL PROTEIN LEVELS IN THE BLOOD AND CEREBROSPINAL FLUID IN RHEUMATOID ARTHRITIS

BY

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The results obtained by accurate chemical estimation of the blood and cerebrospinal-fluid (C.S.F.) proteins in 23 cases of severe chronic active rheumatoid arthritis are described in the following paper.

Boland and others (1948) reviewed the subject authoritatively, pointing out that very few studies on the C.S.F. proteins in cases of rheumatoid arthritis had been published. They were able to quote only four, and only one other additional study (Sundelin, 1947) appears to exist apart from our own.

Graber-Duvernay and Gerbay (1939) studied the C.S.F. in eighteen cases of " chronic polyarthritis " (most, if not all, probably being cases of rheumatoid arthritis), and found a raised protein level in the C.S.F. of all but one. They concluded that the protein level in the C.S.F. paralleled the activity of the disease and that the estimation of it was more useful as a guide to progress and therapy than the erythrocyte sedimentation rate.

Piaggio Blanco and Sciuto (1941) studied the C.S.F. in 21 cases of " sciatica of vertebral origin ". Boland and others (1948) consider that seven of these cases were probably suffering from " rheumatoid spondylitis " (ankylosing spondylitis). In five the protein level in the C.S.F. was raised, with results ranging from 59 to 100 mg. per 100 ml.

Ludwig and others (1943) did various biochemical estimations on the C.S.F. in 101 patients, 59 of whom had rheumatoid arthritis and 42 ankylosing spondylitis with or without peripheral joint involvement.

Taking 45 mg. protein per 100 ml. C.S.F. as the upper limit of normal, they found a raised total protein (46 to 70 mg.) in 6·8 per cent. of the rheumatoid arthritics, and in 28·6 per cent. of the ankylosing spondylitics (range 47 to 105 mg.). They found no correlation between the level of protein in the C.S.F. and the erythrocyte sedimentation rate, the severity of the disease process, and its duration, although there seemed to be some correlation with the activity of the disease.

Polley (1945) found a raised C.S.F. protein level in three out of 24 cases of " rheumatoid spondylitis ".

Boland and others (1948) studied fifty cases of ankylosing spondylitis, seventeen with peripheral joint involvement. The C.S.F. protein estimations were done

by the method of Johnston and Gibson (1938), a non-specific colorimetric test. They accept the range of normal C.S.F. protein as 15 to 45 mg. per 100 ml. and they found an increased C.S.F. protein level (46 to 98 mg.) in 21 cases (42 per cent.). The blood protein (method of estimation not given) was slightly raised (over 8 g.) in four cases, and in only one of the four was the C.S.F. protein raised. They conclude there is no correlation between the blood and C.S.F. protein levels, or between the latter and the severity or duration of the disease process. They also conclude that:

(1) the spine need not be affected to have a raised C.S.F. protein level and hence the meninges are not necessarily the source of the protein,
(2) the choroid plexus is perhaps unduly permeable to protein in cases of rheumatoid spondylitis,
(3) the protein may possibly enter the C.S.F. by way of perivascular and perineural channels,
(4) the estimation of the C.S.F. protein in cases of rheumatoid spondylitis is of little clinical value.

Sundelin (1947) studied the total and differential protein levels in the C.S.F., by the method of Izikowitz (1941), in 141 cases of rheumatoid arthritis, three of whom had " rheumatoid spondylitis ". The results were analysed carefully in great detail in an endeavour to correlate the protein changes with the severity or duration of the disease process. The abnormality of the C.S.F. protein level found was approximately proportional to the severity, and inversely proportional to the duration, of the disease, but the findings were not highly significant. Sundelin found a raised total protein level in 58 cases (35·1 per cent.).

Izikowitz (1941) estimated the proteins in the C.S.F. in 72 normal persons by an accurate chemical method of his own (modified micro-Kjeldahl). His figures give a wider range of normal than is normally accepted, but there seems little doubt of their accuracy (Tables II and III). Sundelin's findings are keyed to these figures, but those of other workers are not, so that the percentage of abnormals reported in other workers' papers appears unduly high. No one has reported a C.S.F. protein level in uncomplicated rheumatoid arthritis more than half as high again as the upper limit of normals so that the abnormalities reported are not very marked.

Eeg-Olofsson (1948) using Izikowitz's method found it less accurate than Izikowitz claims, but even so the error was no more than about 1 per cent.

Estimation	Standard Errors (mg. per cent.)	
	Izikowitz (1941)	Eeg-Olofsson (1948)
Total Protein	±0·17	±1·4
Globulin	±0·08	±0·39
Albumin	±0·14	±1·0

We consider that the disease process in ankylosing spondylitis is not the same as that in rheumatoid arthritis. All the previous investigations, except that of

Graber-Duvernay and Gerbay (1939), come from the other side of the Atlantic, where the opposite view is held, and their findings have been reviewed in that light. The figures of Ludwig and others (1943) and Sundelin (1947) were thus the only ones we felt could be safely taken as indicating the findings to be expected in cases of what we term rheumatoid arthritis.

Present Investigation

The results just mentioned indicated that a high C.S.F. protein level or alterations in the differential protein content in the C.S.F. occur in a proportion of cases of rheumatoid arthritis.

It has long been known that plasma total and differential protein levels may be abnormal in the majority of long-standing or severe cases of rheumatoid arthritis, the commonest findings being a low total protein level and increased levels of globulin and fibrinogen (Fletcher, 1947) or various combinations of the above. It is not altogether certain whether the low total protein reported by many observers is due to rheumatoid arthritis *per se*, or to undernutrition, resulting from the fact that many of these patients have a poor appetite and, because of their locomotor disability, are unable to get about to do the shopping and cooking, and thus in many cases may live on little more than bread-and-butter, tea, and jam. This fact has been eliminated in the present study, because all cases were on adequate hospital diet for several weeks before the investigation.

It was thought of interest to compare the findings in the blood and C.S.F. to see if any light could be thrown on the aetiology of rheumatoid arthritis (Sundelin's study was undertaken because he thought that there was much clinical evidence that rheumatoid arthritis was, in part, at least, a disease of the central nervous system). In the present study the blood (serum) and C.S.F. total and differential proteins have been estimated by an accurate chemical method.

Lumbar puncture is not a procedure to be embarked upon lightly, so it was considered advisable to do a pilot experiment before embarking on a large-scale investigation. Hence only chronic active severe cases have been studied, for it was thought that the changes, if any, would be most marked in such cases, and hence most easily detected.

Clinical Criteria

Diagnosis of Rheumatoid Arthritis.—Polyarticular destructive arthritis, involving the small joints (metacarpophalangeal and proximal interphalangeal) of the hands in all cases; constitutional upset (loss of weight, weakness, and fatiguability); raised E.S.R.; characteristic radiological appearances of juxta-articular osteoporosis, loss of joint space, and erosions of the joint surface (the last symptom was not present in all, and all patients were afebrile).

Chronicity.—More than 4 years since onset of symptoms and signs of disease (range 4 to 15 years; average 7·4 years).

Severity.—Involvement of nearly all limb joints (spine involved in none of the cases); marked constitutional upset; E.S.R. over 30 mm. first hour (Westergren), highest reading 140 mm. first hour; marked crippling; radiological or clinical evidence of subluxation or ankylosis of joints.

Activity—joints hot, swollen, and painful; marked radiological evidence of decalcification; combination of high E.S.R. and iron-resistant anaemia.

Age and Sex.—The patients' ages ranged from 23 to 69 years (average 52). There were twelve females (aged 23 to 64 years, average 48) and eleven males (aged 42 to 69 years, average 56·3).

Experimental Details.—In accordance with the view that the constitution of the C.S.F. varies with the level from which it is taken (Izikowitz, 1941) it was considered advisable to do all lumbar punctures at the same level—between L3 and L4. All punctures were done without any premedication and in the lateral position.

The blood and C.S.F. samples were taken at the same time, and sent to the laboratory in plain bottles, and the protein estimations were begun at once.

Methods

ANALYSIS.—All determinations of the proteins were done by the micro-Kjeldahl method. The globulin was precipitated from the blood serum by 42 per cent. (W/V) crystalline sodium sulphite (Campbell and Hanna, 1937). The procedure adopted for the precipitation of the proteins from C.S.F. was that used by Izikowitz (1941), but the method was altered so that the combusted protein could be treated in the same way as the blood serum proteins. Though, in blood, fractionation of the proteins by half-saturation with ammonium sulphate gives slightly higher results for the albumin than when 42 per cent. (W/V) crystalline sodium sulphite is used, it was thought advisable not to change the Izikowitz method of globulin precipitation as we intended to relate our results to those obtained by Izikowitz in his studies of the C.S.F. proteins in normal subjects. The technique used was as follows:

Blood

Total Protein.—0·5 ml. serum was diluted to 10 ml. with water. 2·5 ml. of this mixture was taken, 2·5 ml. water added, and the protein precipitated by 0·2 ml. 7·5 per cent. sodium molybdate and 0·2 ml. 2/3 N sulphuric acid. After spinning this mixture for 5 mins., the supernatant fluid was decanted and the tube allowed to drain on filter paper. The protein was then heated with 1·5 ml. digestion reagent (50 per cent. sulphuric acid containing 1 per cent. selenium dioxide). Heating was continued until the mixture cleared and then for one hour after.

Albumin.—0·5 ml. serum was diluted to 10 ml. with 42 per cent. (W/V) crystalline sodium sulphite, and after 15 mins. at room temperature the mixture was filtered through a No. 42 Whatman paper. 2·5 ml. of the filtrate was taken, and 2·5 ml. water and 2·5 ml. 10 per cent. sulphuric acid added. To drive off the sulphur dioxide liberated from the sodium sulphite the tube was shaken and, if necessary, warmed slightly. The protein was precipitated by adding 0·5 ml. 7·5 per cent. sodium molybdate. The mixture was spun and the tube drained as before. Digestion was carried out in the same way as for total protein.

Globulin.—This was calculated by subtracting the albumin from the total protein.

Cerebrospinal Fluid

Total Protein.—2 ml. C.S.F. were diluted to 17 ml. with 10 per cent. trichloracetic acid. After mixing, the tube was placed in a water-bath at 56° C. for 60 min. to precipitate the protein. It was then centrifuged for 45 min. and the supernatant fluid decanted. The precipitate was washed with 17 ml. 9 per cent. trichloracetic acid and centrifuged again for 30 min. Combustion was carried out as for blood proteins.

Albumin and Globulin.—The globulin was precipitated from 5 ml. C.S.F. by the addition of 5 ml. of a saturated solution of ammonium sulphate. After mixing, the tube was placed in a water-bath at 56° C. for 60 min. and then centrifuged for 45 min. 4 ml. of the centrifugate was taken for the albumin estimation. The precipitate was dissolved in 4 ml. water and 13 ml. 10 per cent.) trichloracetic acid was added to re-precipitate the protein. The tube was incubated at 56° C. for 60 min. and then centrifuged for 45 min. The supernatant fluid was poured off, the tube drained, and the precipitate washed with 17 ml. 9 per cent. trichloracetic acid. The tube was re-centrifuged for 30 min. This washing was repeated. Combustion was carried out as for blood proteins.

For the albumin determination 13 ml. (10 per cent.) trichloracetic acid were added to 4 ml. of the centrifugate (from globulin fractionation). The tube was placed in a water-bath at 56° C. for 60 min. and then centrifuged for 45 min. The supernatant fluid was decanted and the precipitate washed with 17 ml. 9 per cent. trichloracetic acid and centrifuged again. This washing was repeated making two washings altogether. The protein was combusted in the same way as the blood proteins.

In all the C.S.F. protein estimations, the tubes were thoroughly drained and the inside of each dried with filter paper after they had been centrifuged.

DISTILLATION.—5 ml. 40 per cent. caustic soda (W/V) was used for the liberation of the ammonia and the distillate was collected in N/70 sulphuric acid, 10 ml. N/70 sulphuric acid being used for the blood proteins and 2 ml. N/70 sulphuric acid (measured from the burette used for the final titration) for the C.S.F. proteins. The excess acid was titrated against N/70 sodium hydroxide. A 10-ml. burette was used for the blood proteins and a 2-ml. burette graduated in hundredths for the C.S.F. proteins. The factor 6·25 was used to convert nitrogen to protein values.

CHECK ON ACCURACY OF RESULTS.—The following precautions were taken.

Blood Proteins.—All estimations were done in duplicate.

C.S.F. Proteins.—Where the quantity of C.S.F. allowed the total protein estimations were done in duplicate. Two 4-ml. portions of filtrate from the globulin fractionation were taken for estimation of the albumin. The globulin was always estimated as a further check; results agreed to about 1 per cent.

Normal Values

There is very little in the literature about the absolute values of the differential protein levels in the C.S.F. There are plenty of crude tests indicating an excess of the globulin moiety, but no absolute figures for normal apart from these of Izikowitz (1941). In view of this we have no other course than to accept his values (Tables II and III) in spite of the fact that the total protein figures disagree with those of most workers. Izikowitz's method has been used in this investigation.

Results

The C.S.F. pressure was normal in all our cases, as in all previously reported cases. All relevant results are given in Table I (overleaf). They are grouped for comparison with Izikowitz's figures for normal cases in Tables II and III.

Discussion

Table II shows that the mean C.S.F. total protein levels in rheumatoid arthritis cases of both sexes are similar and above the normal mean. The increase is

TABLE I

CONSOLIDATED RESULTS SERUM (g. per cent.) AND C.S.F. (mg. per cent.)* TOTAL AND DIFFERENTIAL PROTEINS

Case No.	Sex	Age	Total Proteins		Albumin		Globulin	
			Serum	C.S.F.	Serum	C.S.F.	Serum	C.S.F.
2	F	40	9·6	57	3·4	36	6·2	20
1	F	65	9·4	90	4·1	60	5·3	30
7	M	69	7·7	56	3·6	38	4·1	18
17	M	53	7·7	62	4·8	42	2·9	20
5	F	47	7·6	58	4·2	47	3·4	12
13	F	60	7·5	35	4·8	30	2·7	5
16	M	65	7·5	39	3·9	27	3·6	12
8	F	39	7·4	31	4·7	26	2·7	5
10	F	23	7·4	31	4·7	25	2·7	6
12	F	36	7·4	33	4·1	27	3·3	6
14	F	40	7·2	31	4·4	23	2·8	9
6	M	52	7·1	39	4·0	31	3·1	8
9	M	53	7·1	55	3·6	43	3·5	12
11	F	55	7·1	33	4·2	28	2·9	5
3	F	64	7·0	38	4·2	30	2·8	8
22	M	42	7·0	39	5·0	33	2·0	6
23	M	60	7·0	32	4·3	25	2·7	7
21	F	50	6·9	34	4·2	28	2·7	6
20	F	63	6·8	32	4·5	25	2·3	7
4	M	57	6·7	53	4·3	36	2·4	17
18	M	52	6·4	26	3·2	17	3·2	9
19	M	49	6·3	24	4·0	19	2·3	5
15	M	67	6·0	29	3·0	12	3·0	17

* Apparent discrepancies are due to taking C.S.F. figures to the nearest whole number.

significant only in the female cases, although not markedly so. The mean C.S.F. globulin is raised in both sexes, but to a significant degree only in the male cases. The mean C.S.F. albumin is normal in the male cases and significantly raised in the female cases. The mean C.S.F. G/A ratio is significantly increased.

The total protein serum levels are within normal limits except in two cases where they were found to be rather high. No clinical reason for this was evident. The serum albumin figures were normal, but the serum globulin figures and the serum G/A ratio were both high in nearly all cases (Table IV).

The correlation between the serum total proteins and serum globulin is very high, whereas it is almost nil between the serum total proteins and serum albumin. From this it may be deduced that high serum protein levels in these cases are due solely to the globulin fraction (Table V).

As might be expected serum albumin and globulin are inversely related. Serum albumin is not correlated to a significant degree with anything else.

Serum protein levels are significantly correlated with both C.S.F. albumin and globulin levels, as well as C.S.F. total protein levels. The C.S.F. albumin levels are significantly related to the C.S.F. globulin, which suggests that abnormalities have the same cause in both. The serum and C.S.F. globulin levels are significantly correlated. The C.S.F. total protein figures in the rheumatoid arthritis cases show quite a wide range in view of the fact that the cases were essentially analogous.

TABLE II
MEAN OF RESULTS IN NORMAL CONTROLS AND RHEUMATOID ARTHRITIS PATIENTS

Cerebrospinal Fluid		Normal Controls (Izikowitz) N. Mean± Standard Error (mg. per cent.)	Rheumatoid Arthritis Patients N. Mean± Standard Error (mg. per cent.)	Difference± Standard Error (mg. per cent.)
Total Protein	Male	39·46±1·2 (45)*	40·64±3·89 (11)	1·18±4·1 NS
	Female	30·99±1·16 (27)	42·5 ±4·89 (12)	11·51±5·0 S
Globulin	Male	7·71±0·30 (45)	11·82±1·56 (11)	4·11±1·59 S
	Female	6·27±0·29 (27)	10·00±2·10 (12)	3·73±2·12 NS
Albumin	Male	31·74±1·03 (45)	29·2±3·26 (11)	2·54±3·42 NS
	Female	24·80±0·91 (27)	32·5 ±3·0 (12)	7·70±3·11 S
G/A Ratio†	Combined Male and Female	0·245±0·006 (72)	0·373±0·053 (23)	0·128±0·055 S

* Figures in brackets represent number of persons in each group.
NS = not significant. S = significant.
† G/A ratio given in all Tables rather than A/G for ease of comparison with Izikowitz's figures.

TABLE III
EXTREME PHYSIOLOGICAL LIMITS
(from Izikowitz)

Cerebrospinal Fluid	Males (mg. per cent.)	Females (mg. per cent.)
Protein	14-65	13-49
Globulin	2-14	2-11
Albumin	11-52	11-38
G/A Ratio	0·14-0·34	0·14-0·36

It has not been found possible to correlate this variation with the clinical findings or the course of the disease, which confirms the view of Boland and others (1948) that the estimation of the C.S.F. proteins in rheumatoid arthritis is of little clinical importance.

To summarize, the abnormality in the serum appears to be due to the globulin fraction, but variations in the C.S.F. total protein, albumin, and globulin fractions, occur simultaneously and in the same direction. It is difficult to think of any explanation for this, except that, as suggested by Boland and others (1948), the haemato-encephalic barrier is unduly permeable in rheumatoid arthritis, with the result that some serum protein of high G/A ratio leaks into the C.S.F., thus producing a rise in C.S.F. total proteins, both albumin and globulin. Increase in the C.S.F. globulin will be more evident because of its lower normal level and because of the high G/A ratio of the entering proteins.

The regrettable lack of normal controls limits the conclusions which can be

TABLE IV
SERUM AND CEREBROSPINAL FLUID G/A RATIOS

Case No.	Sex	Serum	Cerebrospinal Fluid
1	F	1·3/1	0·5/1
2	F	1·79/1	0·56/1
3	F	0·67/1	0·27/1
4	M	0·56/1	0·46/1
5	F	0·8/1	0·25/1
6	M	0·77/1	0·26/1
7	M	1·14/1	0·48/1
8	F	0·59/1	0·19/1
9	M	0·97/1	0·28/1
10	F	0·59/1	0·24/1
11	F	0·71/1	0·18/1
12	F	0·83/1	0·22/1
13	F	0·56/1	0·17/1
14	F	0·63/1	0·37/1
15	M	1/1	1·43/1
16	M	0·91/1	0·43/1
17	M	0·59/1	0·48/1
18	M	1/1	0·53/1
19	M	0·59/1	0·26/1
20	F	0·53/1	0·28/1
21	F	0·63/1	0·21/1
22	M	0·4/1	0·27/1
23	M	0·63/1	0·28/1

drawn. Nevertheless, it is felt that the results obtained have yielded some useful information. It is particularly unfortunate that so little is known about the absolute values for the albumin and globulin ratios in the C.S.F. Pemberton (1935) suggested that the capillaries may be abnormal in rheumatoid arthritis, and it is possible that local vascular derangement may be important in producing some of the symptoms and signs of the disease, although it seems unlikely that this is of basic importance in the aetiology.

One possible explanation of the changes in the serum protein is that some degree of liver dysfunction is present in rheumatoid arthritis. Swanson (1949) found

at some time or other abnormal serum colloidal gold reactions, in approximately half of 72 cases of rheumatoid arthritis, and he quotes other authorities as finding abnormal serum colloidal gold reactions in up to 76 per cent. of cases. Another possible reason for the appearance of excess globulin is that it comes from the lymphocytes (Dougherty and White, 1947), being an antibody response to an unknown causative antigen.

TABLE V

CORRELATION COEFFICIENTS

Total Proteins Serum / Total Proteins C.S.F.	0·734 S
Total Proteins Serum / Albumin Serum	0·075 NS
Total Proteins Serum / Albumin C.S.F.	0·702 S
Total Proteins Serum / Globulin Serum	0·839 S
Total Proteins Serum / Globulin C.S.F.	0·594 S
Total Proteins C.S.F. / Albumin Serum	0·027 NS
Total Proteins C.S.F. / Albumin C.S.F.	0·942 S
Total Proteins C.S.F. / Globulin Serum	0·652 S
Total Proteins C.S.F. / Globulin C.S.F.	0·835 S
Albumin Serum / Albumin C.S.F.	0·181 NS
Albumin Serum / Globulin Serum	—0·480 S
Albumin Serum / Globulin C.S.F.	—0·340 S
Albumin C.S.F. / Globulin Serum	0·510 S
Albumin C.S.F. / Globulin C.S.F.	0·634 S
Globulin Serum / Globulin C.S.F.	0·704 S
G/A Serum / G/A C.S.F.	0·47 S

These results provide further confirmation for the current idea that rheumatoid arthritis is a generalized disease (Ellman and Ball, 1948).

Summary

(1) The literature on C.S.F. protein in rheumatoid arthritis is reviewed.

(2) The total and differential serum and C.S.F. protein was investigated in 23 cases of chronic active severe rheumatoid arthritis with the following results:

(*a*) serum globulin and G/A ratio were found to be significantly increased.
(*b*) high C.S.F. total protein level correlated with high serum protein level.
(*c*) high C.S.F. globulin and G/A ratios were common findings.

(3) It was not possible to correlate the results with the clinical findings. It is concluded that the estimation of the C.S.F. protein is of no clinical importance.

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Taux total et différentiel des Protéines du Sang et du Liquide Céphalo-rachidien dans l'Arthrite Rhumatismale

Résumé

(1) Les auteurs passent en revue la littérature sur les recherches concernant les protéines du L.C.R. dans l'arthrite rhumatismale.

(2) Le taux des protéines, total et différentiel, dans le sérum et dans le L.C.R. fut déterminé dans 23 cas d'arthrite rhumatismale chronique, active et grave, et les résultats suivants furent obtenus:

(*a*) augmentation appréciable dans le sérum de la globuline et du rapport globuline/albumine;
(*b*) taux élevé des protéines totales du liquide céphalo-rachidien en corrélation avec le taux des protéines sériques;
(*c*) taux de la globuline et le rapport globuline/albumine dans le L.C.R. augmentés.

(3) Il n'a pas été possible de trouver un rapport entre ces résultats et le tableau clinique et on en conclut que la détermination des protéines du L.C.R. n'a pas d'importance clinique.

Cifras totales y diferenciales de Proteinas de la Sangre y del Líquido Céfalorraquídeo en la Artritis Reumatoide

Resumen

(1) Los autores pasan en revista la literatura sobre las investigaciones respecto a las proteinas del líquido céfalorraquídeo en la artritis reumatoide.

(2) Las cifras de la proteina, total y diferencial, en el suero y en el líquido céfalorraquídeo fueron determinadas en 23 casos de artritis reumatoide crónica, activa y grave y los resultados siguientes fueron obtenidos:

(*a*) aumento notable en el suero de la globulina y de la razón globulina/albumina;
(*b*) cifra alta de las proteinas totales del líquido céfalorraquídeo en proporción con el aumento de las proteinas del suero;
(*c*) cifra de la globulina y la razón globulina/albumina en el líquido céfalorraquídeo aumentadas.

(3) No se pudo establecer relación entre estos resultados y los resultados clínicos. En conclusion, la determinación de las proteinas del líquido céfalorraquídeo no tiene importancia clínica.

FURTHER INVESTIGATIONS ON PITUITARY GLAND IMPLANTATIONS IN RHEUMATOID ARTHRITIS

BY

GUNNAR EDSTRÖM and STIG THUNE

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Experiences in the Arthritis Department of the University Hospital, Lund, of pituitary gland implantations in cases of rheumatoid arthritis have been previously reported in this journal (Edström, 1950a). Now that another hundred cases have been treated in the department, the period of observation since the operations has become longer, and the operative technique somewhat modified, and it is possible to present a further report.

Technique

(1) The following technique was employed in all the cases reported below:

Fresh anterior lobes of pituitary glands from calves and pigs were used. Immediately after the animals were killed the heads were taken to the hospital. The anterior lobes were excised aseptically in a preparation room adjacent to the operation room. The heads were fixed in a special position and flayed, the skull was sawn off and the brain taken out. Using sterile gloves, the surgeon exposed and excised the pituitary gland with the adjoining pedicle, including as much as possible up towards the tuber cinereum. The posterior lobe was then cut off. The hypophyses were usually divided into two parts.

Under local anaesthesia a deep incision, 1·5 to 2 cm. long, was made in the skin, down into the gluteal muscles, or laterally in the thigh muscles. A 9 cm. long-nose speculum was introduced and two or three of the split hypophyses were implanted. The skin was then sutured.

The time that elapsed between the killing of the animals and the re-introduction of the anterior lobes of the pituitary glands into living tissue was approximately 30 minutes, and never exceeded 45 minutes.

(2) We also tried another method whereby the lobes were reduced to a pulp and injected by means of a large-aperture needle. This procedure, however, is no good if a foreign-body reaction occurs. There is then a considerable amount of detritus, which requires a considerable time to be eliminated, even if the reaction is mild and there is no growth of pathogenic bacteria. When the fragments are introduced whole they are more easily expelled, and the reaction is inconsiderable and only lasts a day or two, particularly when it is alleviated by means of some antihistamin preparation.

(3) In the last two months we have tried a new technique, partly in accordance with that used in Vienna by Fellinger (1950a, b), who introduced a modification by freezing the hypophyses after slaughter until they are used for implantation.

In the slaughter-house in Kävlinge, which supplies us with hypophyses, the glands are taken from practically every pig for delivery to pharmaceutical factories for the preparation of ACTH. The slaughtering is carried out by the conveyor-belt system, which deals with approximately 150 animals per hour. Five minutes later, when the bodies

are scalded and the viscera removed, they reach a man with a revolver-shaped apparatus provided with a rotating sawing barrel. With this instrument he removes from the ventral side of the skull a cylindrical mass with the hypophysis in the middle. Opposite him stands a technician who excises the hypophyses with a pincette and places them in a small container surrounded by ice. When the hypophyses are destined for our laboratory, the technician using a sterile pincette selects those that have not been contaminated by the rotating cylinder. These are then collected in an aseptic Petri dish, which is immediately placed between two packings of solid CO_2 in a specially-constructed thermos flask (the temperature being below —20° C.). The flask is then taken to the hospital where it is kept in a refrigerator until the operations are to be performed. When the hypophyses are taken out again they are like hard-frozen marbles, and are therefore allowed to thaw for 6 or 7 min. in a 0·1 per cent. septin (quaternare ammonium compound) solution before being implanted in the manner previously described. By this method four to seven hypophyses are usually used in one operation.

According to our calculations based on observations of the practical application of this freezing method as a step in the mechanized system in the slaughter-house, about 15 minutes elapse between the killing of the animal and the placing of the hypophyses in the thermos flask. In our experience an instantaneous freezing like the one mentioned by Fellinger (1950a, b) cannot be realized in a large slaughter-house, and we believe it to be practically impossible even in a small one. Judging from tests made in the clinic, a combined freezing and thawing time of 25 to 30 min. seems to be permissible without impairing the biological effect.

Clinical and Biochemical Effect

Clinical effect, when present, almost always occurred during the first 2 days following the first implantation, and sometimes after later implantations. Objectively, reduced peri-oedema around the affected joints, improved mobility, and a slight euphoria with increased mental capacity and activity, were noted. Subjectively, the patients reported considerably reduced tenderness on moving,

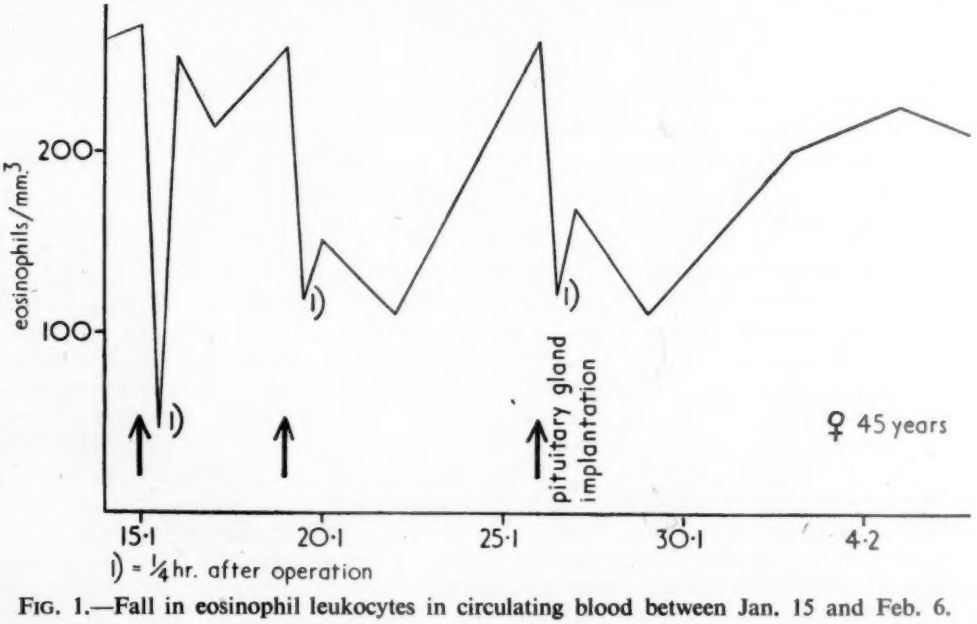

FIG. 1.—Fall in eosinophil leukocytes in circulating blood between Jan. 15 and Feb. 6.

reduced stiffness in both joints and muscles, improved movement, less feeling of being ill—a similar effect to that obtained after the injection of ACTH. The following biochemical changes were noted:

(1) marked fall in the number of eosinophil leukocytes in the circulating blood (usually by much more than 50 per cent.) was seen after 4 hours and lasted for 2 or 3 days (Fig. 1);
(2) approximately twofold increase in 17-ketosteroids in the urine occurred for a 24-hour period (Fig. 2);
(3) reduction of the lymphocytes and an increase in the polynuclear leucocytes during the first 24 hours;
(4) increased excretion of uric acid in the urine during the first 24 hours (Fig. 3);
(5) lowered erythrocyte sedimentation rate, which develops more slowly and does not become pronounced until two weeks later.

There was no certain effect on the electrolytes in the serum and no change in weight.

As will be seen, the effects are, in many respects, similar to those obtained with injections of ACTH, although not so marked or pronounced, particularly from a biochemical point of view. They are, instead, in most cases of longer duration clinically. In order to give a more extensive view of the clinical effect all the cases in which the time of observation following the implantations was at least 9 months, are tabulated below.

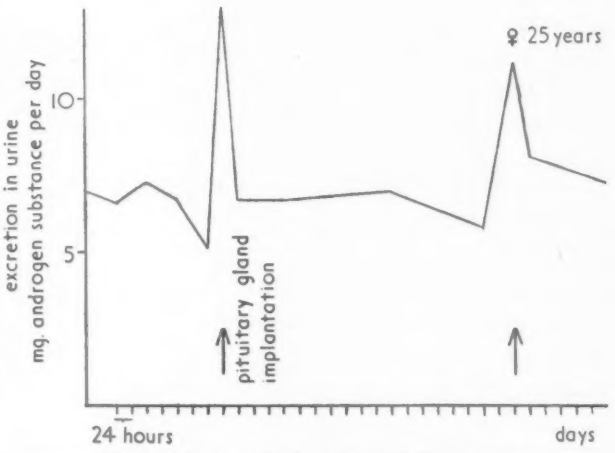

FIG. 2.—Increase in 17-ketosteroid excretion in urine.

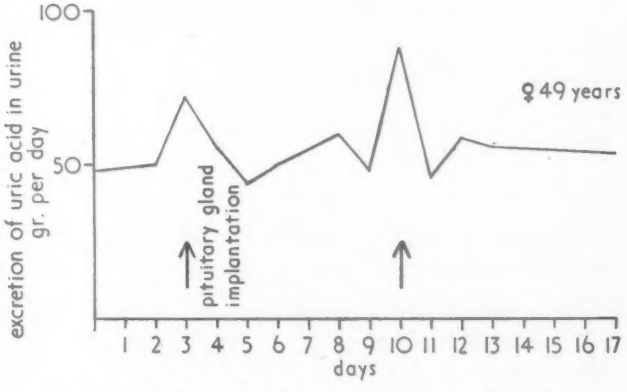

FIG. 3.—Increase in uric acid excretion in urine.

No clinically demonstrable effect was obtained in about 25 per cent. of cases. In another 25 per cent. relapses occurred after a period of 10 to 15 weeks free from symptoms of any existing process. Six of these eleven cases were re-admitted to the hospital and received new implantations (four patients are at present symptom-free, and the other two improved temporarily, but had another relapse). Out of

51 cases, 22 showed clinical effects which have persisted for 9 months, and twenty of these have been entirely free from symptoms of any existing process (Table I).

TABLE I
CLINICAL STATE IN DECEMBER, 1950, OF 51 RHEUMATOID ARTHRITIS CASES IN WHICH PITUITARY GLAND IMPLANTATIONS WERE DONE BETWEEN SEPTEMBER, 1949 AND MARCH, 1950 (IN CHRONOLOGICAL ORDER)

Clinical Effect	Group I	Group II	Group III	Total	Percentage
Total freedom from clinical symptoms ..	4	10	8	22	43
Improvement	2	4	3	9	17
Relapse	2 (4)	2 (4)	3	7 (11)	14 (22)
None	2	5	6	13	26
Total Cases	10	21	20	51	100

Spontaneous relapses are quite common during the course of rheumatoid arthritis. This makes it difficult to evaluate our various kinds of treatment. The cases in question were on the whole of average severity and, with two exceptions, of at least 5 months' duration. Some of them were very malignant and of long duration. When considering these facts the result must be described as satisfactory, at least according to present standards.

The influence of the patients' age is seen in Table II. As a rule the older the patient, the poorer the result. The similarity to the animal experiments of Silberberg and Silberberg (1939, 1940, 1949) is obvious. These investigators observed proliferation of the articular cartilages after implantation of pituitary glands in rats. In older animals the effect was much less common: instead degeneration and reactionary changes often occurred.

TABLE II
SAME MATERIAL AS TABLE I, BY AGE GROUPS*

Clinical Effect	Under 40 Years of Age		40 Years Old or More	
	Cases	Per cent.	Cases	Per cent.
Total freedom from clinical symptoms ..	16	47	6	35
Improvement	7	—	2	—
Relapse	4	—	3	—
None	7	21	6	35
Total Cases	34		17	

* One case 9 years old. three 11 to 18 years, fifteen 20 to 29 years, fifteen 30 to 39 years, sixteen 40 to 49 years, and one 50 years.

Another factor influencing the result is the length of time that the patient has suffered from the disease (Table III, opposite).

Discussion

It is improbable that the effect obtained in these implantations is other than *a transient hormonal shock* from the implanted gland, a stimulation of the adrenal cortex, judging from the biochemical reactions of hardly more than 24-hours'

TABLE III
SAME MATERIAL AS IN TABLES I AND II, BY *DURATIO MORBIS* AT TIME OF FIRST IMPLANTATION

Clinical Effect	*Duratio Morbis**					
	Less than 1 Year		From 1 to 2 Years		2 Years or More	
	Cases	Per cent.	Cases	Per cent.	Cases	Per cent.
Total freedom from clinical symptoms ..	10	59	4	36	8	35
Improvement	1		2		6	
Relapse	3 (5)		2 (3)		2 (3)	
None	3	18	3	27	7	30
Total Cases	17		11		23	

* Duratio morbis in one case 2 months, in one 4 months, in three 5 months (one of these showed no clinical effect), in one 6 months, and in eleven 7 to 11 months.

duration. That it is a prolonged effect of transplantation type, as originally suggested, is quite out of the question; Westman and Jacobsohn (1940, 1942), for example, showed that the implanted anterior lobes of the pituitary glands are necrosed and absorbed rather quickly.

Stimulation of the adrenal cortex can be brought about in different ways. A depression of the eosinophil leukocytes in the circulating blood has been observed after the administration of anaesthesia to a patient. In order to exclude the possibility that the shock of operation itself causes the reactions observed, control experiments have been carried out and pieces of calf brain without any hypophysis have been implanted with the same operative technique. In the control experiments none of the biochemical reactions related above were observed, nor was there any effect on the patient's clinical status.

The stimulation of the adrenal cortex caused by the implanted pituitary glands is not quite parallel to that obtained through injection of ACTH. The effect sets in more slowly and lasts longer. The ACTH-molecule is very small and injected ACTH is excreted very rapidly, principally in the urine. Judging from animal experiments about half the amount is probably excreted within 5 minutes. The optimum stimulation of normal adrenal function is achieved by the injection of 7 to 8 mg. ACTH. The effect of the biologically active hormone produced by the implantate occurs more slowly and continuously during a certain time, probably about 24 hours. This method of administering the hormone is probably better and more effective from a biological point of view. It is not certain whether the effect is caused by the ACTH or by another similar but biologically more effective substance. The amount of ACTH obtained from the same amount of pig or calf hypophyses has increased almost tenfold in the last 2 years because of improved methods of extraction. Everything indicates that it will increase still further and that at present we are ignorant of how much adrenocortico-stimulating substance is contained in one hypophysis. Most probably, ACTH is not the only stimulating substance and these compounds may differ in chemical

form. This would explain the considerable adrenocortico-stimulating effect of a few implanted anterior lobes of hypophyses, although our present methods have disclosed only a small amount of ACTH (viz. 1-3 mg.). The effect seems to be increased when the pedicle towards the tuber cinereum is also included. In this connection one case is of particular interest.

Case 1. A 45-year-old male was treated in September and October, 1949, without effect with three implantations of calf pituitary glands, consisting of two anterior lobes each, at one-week intervals. Then small doses of testosterone were given, likewise without effect. When the dosage was increased to 100 mg. testosterone injected intramuscularly supplemented with 500 mg. ascorbic acid given intravenously twice daily, a certain clinical effect was obtained, which, however, passed off as soon as the dosage was reduced. In October, 1950, this patient was treated with ACTH; on the first day he received 5 mg. eight times, on the second day 5 mg. six times, on the third and fourth days 5 mg. five times. There was a marked clinical and biochemical effect. When the dose was reduced to 5 mg. three times on the fifth day the clinical symptoms reappeared on the sixth day, and the number of eosinophil leukocytes, which had fallen markedly, began to rise again. Clinical effect was not obtained again until a few days later when the ACTH dose was increased to 5 mg. five times a day. It seems as if comparatively high doses of steroid hormones were necessary in this case to obtain clinical effect, and that implantation in such cases cannot produce a sufficiently powerful hormonal shock.

During the year when these implantations were carried out, another ten cases of rheumatoid arthritis were treated with injections of cortisone and ACTH. In two cases, one treated with cortisone and one with ACTH, a prolonged remission of the clinical symptoms was obtained, a result similar to that obtained in twenty of the implantation cases mentioned above.

Case 2. A 12-year-old boy with a particularly malignant rheumatoid arthritis and considerable arthritic exudations. The erythrocyte sedimentation rate was approximately 100 mm. per hour and the temperature subfebrile. This condition had lasted for about 6 months, and neither salicylic acid, large doses of penicillin, sulphonamides, blood-transfusions, or desoxycorticosterone acetate had had any effect. Treatment with cortisone was then initiated: 100 mg. twice daily for 2 days, followed by 50 mg. twice daily for 6 days, 50 mg. once a day for 4 days, and 25 mg. once a day for 2 days. The effect was dramatic. The erythrocyte sedimentation rate fell to 6 mm. per hour and the clinical symptoms disappeared altogether. This condition has now lasted for more than 8 months; the patient has still completely normal joints and there are no symptoms from the heart or other organs.

Case 3. A 4-year-old boy, who had suffered from an extremely malignant rheumatoid arthritis with marked changes in the joints, high erythrocyte sedimentation rate, and subfebrile temperature for the past year, and had not responded to any therapy whatsoever (Edström, 1949). In September, 1949, he received ACTH for a little more than 2 weeks with an average dose of 15 mg. three times a day. During the treatment he was seen to move more easily and he complained less of pain. However, no reduction in the exudation or peri-oedema of the joints was observed, nor was there any change in temperature which remained around 38° C., sedimentation rate, or pulse. About 10 days after the completion of the injections, however, the picture changed. For 3 days the temperature sank gradually to normal values (36·7°-37·1° C.). At the same time the exudation and peri-oedema around the affected joints disappeared. This was particularly noticeable on the hands and feet. The patient began to move like a normal child. The effect on the sedimentation rate came more slowly and was only slight during the first weeks.

About 4 weeks after being discharged from the hospital the patient fell ill at home

with acute tonsillitis. He had a recurrence of polyarthritis symptoms which, however, lasted only 2 weeks. After that the erythrocyte sedimentation rate continued to fall, the patient increased in weight and improved more and more. In May and December, 1950, he had a catarrhal infection, but no recurrence of the rheumatoid syndrome.

Though not completely free from symptoms, he is afebrile and is playing and running about, more or less like other children. The wrists and insteps are somewhat thickened, but there is no tenderness. Both the boy and his parents are satisfied with this comparatively quiet and agreeable condition, which has now lasted for more than one year.

Similar delayed results after injections of ACTH were observed by Waldenström (1950). In two cases of the pituitary gland implantations reported here the clinical effect did not occur until 2 weeks after the implantation.

Westman (1949) reported the delayed results of a series of 246 cases of *endocrine disturbance* in which implantation of the anterior lobes of pituitary glands had been carried out, all of which had been followed for more than one year. In a fairly large number a persistent effect was obtained. Similar results have been described by Nystrand (1947) and Kylin (1937, 1943). There are also recent reports of implantation being attempted in other conditions. At the hospital in Lund a few cases of disseminated sclerosis have been treated and the effect lasted for about three months. Svartz (1949) described a case of lupus erythematosus from the Karolinska Sjukhuset in Stockholm, where implantation was tried with satisfactory results. At a congress held at Bad Gastein, Austria, in September, 1950, Fellinger, of Vienna, gave an account of more than 1,000 cases, predominantly of rheumatoid arthritis, in which he had made pituitary gland implantations with much the same results as ours. In his series, however, relapses occurred more commonly and more rapidly than in our material. One of us (G.E.) talked with a colleague who had been treated by Fellinger for severe rheumatoid arthritis of many years duration, and who reported that he had not felt so well in many years as during the 3 months immediately following the implantations. He said that later the symptoms reappeared, but he still considered himself much improved after the implantations. We have received numerous reports by letter from clinics in different countries, and, on the whole, the experiences described are similar to ours. In older patients improvement is rare, and relapses are frequent, although they do not usually occur until 2 to 4 months after treatment.

The present findings should stimulate further research. A new method should be sought by which a hormone-depot, or prolonged effect of ACTH or of extract from the anterior lobes of the pituitary gland, can be obtained.

Summary

Implantations of anterior lobes of the pituitary gland of pigs or calves have been made in about 100 cases of rheumatoid arthritis in the Arthritis Department of Lund Hospital. Fresh pituitary glands were used, as it is important that the procedure be carried out rapidly. Lately, attempts have been made to preserve the fresh hypophyses by deep-freezing.

Of the 100 cases, 51 were observed for 9 months after treatment. Approximately half (27 cases) of this group are still without clinical symptoms or considerably

improved, twenty having been totally free from clinical symptoms; eleven have had relapses, generally after about 3 months, and thirteen showed no clinical effect. As a rule, the older the patient, the poorer the result.

The clinical effect, when it occurred, usually manifested itself immediately after the operation. The increased excretion of 17-ketosteroids and uric acid usually disappeared within 24 hours; the reduction of the number of eosinophil leukocytes in the circulating blood, which was marked after 4 hours, sometimes lasted 2 or 3 days. Other biochemical reactions were uncertain and less marked.

The results, though not remarkable, seem to be of scientific interest. A method must be sought whereby the effect of ACTH can be prolonged.

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La Greffe de la Glande Pituitaire dans l'Arthrite Rhumatismale

RÉSUMÉ

Des greffes de lobe antérieur de l'hypophyse de porc et de veau furent effectuées dans à peu près 100 cas d'arthrite rhumatismale au Départmente d'Arthrite de l'Hôpital de Lund. Des hypophyses frais furent utilisés, car il est important que l'opération soit exécutée rapidement. Récemment on avait essayé de conserver la fraicheur des glandes en les congélant.

Sur ces 100 cas, 51 durent suivis pendant 9 mois après le traitement. On nota une amélioration considérable chez la moitié d'entre eux (27), avec absence totale de symptômes cliniques chez 20; il y eut des rechutes chez 11, généralement 3 mois environ après les greffes; l'effet clinique fut nul chez 13.

L'effet clinique, quand il se produisait, se manifestait généralement immédiatement après l'opération. L'excrétion augmentée des 17-cétostéroïdes et de l'acide urique devenait normale généralement au bout de 24 heures; la diminution du taux des éosinophiles, prononcée au bout de 4 heures, persistait quelquefois pendant un ou deux jours. D'autres réactions biochimiques étaient inconstantes et peu prononcées.

El Injerto de Glándula Pituitaria en Casos de Artritis Reumatoide

RESUMEN

Injertos de lóbulos anteriores de glándulas pituitarias de cerdo o ternero han sido realizados, en el Departamento de Artritis del Hospital de Lund, en cerca de 100 casos de artritis reumatoide. Las glándulas pituitarias fueron usadas frescas, siendo importante que la operación se realice rapidamente. Ultimamente se han hecho tentativas para preservar frescas las hipófisis, mediante congelación. De los cien casos, 51 fueron observados por nueve meses después del tratamiento. Aproximadamente la mitad de este grupo (27), se encuentran todavía sin síntomas clínicos o considerablemente mejorados—20, enteramente libres de síntomas clínicos. 11 casos han tenido recaídas, generalemente con tres meses de posterioridad a los injertos, y (13) no demostraron efectos clínicos.

Los efectos clínicos, cuando ocurrieron, se manifestaron usualmente inmediatamente después de la operación. El incremento de la secreción del ácido úrico y de los 17-cetoesteroides generalemente desapareció dentro de las primeras 24 horas; la diminución de la cifra de los eosinófilos en la corriente sanguínea, notable después de 4 horas, algunas veces duró uno o dos días. Otras reacciones bioquímicas fueron inciertas y poco pronunciadas.

DESOXYCORTICOSTERONE ACETATE (DOCA) AND VITAMIN C IN RHEUMATOID ARTHRITIS*

BY

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Among various products studied on account of the similarity of their chemical formulae to that of cortisone, we have progesterone, testosterone, compound S, 17-hydroxy-pregnenolone, several other steroids, listed at present by code letters: MK-08, MK-11, MK-14, MK-18, MK-20; and finally, desoxycorticosterone with vitamin C.

Lewin and Wassén (1949) first reported the effects of combined injections of desoxycorticosterone acetate (DOCA) and ascorbic acid in rheumatoid arthritis. This treatment has been repeated with contradictory results, extraordinary success having been reported by some workers, while others emphasized the inefficacy of the method.

We have used this treatment with 22 patients, and our results form the subject of this communication.

Material

The 22 patients were affected with rheumatoid arthritis in the active stage, diagnosis being confirmed by clinical and laboratory findings. There were fourteen females and eight males. The duration of the disease on beginning the treatment varied from 3 months to 15 years, and the patients' ages from 24 to 62 years. The severity of the disease varied from slight pain with little functional limitation (+), to severe pain with complete functional disability (+ + + +). The duration of the treatment ranged from 12 to 86 days.

Technique

We used the original technique described by Lewin and Wassén, consisting in the intramuscular injection of 5 or 10 mg. desoxycorticosterone acetate in oily solution, followed immediately by the intravenous injection of 1 g. ascorbic acid (10 ml. of a 10 per cent. solution). Where the intravenous route was not possible the ascorbic acid was injected intramuscularly. To give a more accurate interpretation and to eliminate psychogenic influences, we used in the few cases where good results seemed to be obtained, some placebo phials containing sesamoid oil of exactly the same appearance as those containing desoxycorticosterone acetate.

Results

Clinical.—Of the 22 patients treated, fourteen showed no substantial change, either objective or subjective, during or after the treatment. Four improved, but of these, only one can be considered as a real improvement (Case 10), inasmuch as of the remaining three, two (Cases 7 and 15) were relieved only subjectively

* We are indebted to the Ciba Laboratories for samples of Percorten and placebo phials, and to the Merck Laboratories for samples of Cebion.

CLINICAL AND LABORATORY RESULTS OBTAINED IN TWENTY-
WITH DESOXYCORTICOSTERONE

Case No.	Sex	Age (years)	Disease		Daily Dosage		
			Duration (years)	Severity	DOCA (mg.)	Ascorbic Acid (g.)	
						Intramuscular	Intravenous
1	F	37	4	++	5	—	1
2	F	42	2	+++	5	—	1
3	M	28	1½	++	5	—	1
4	F	43	10	++++	5 (44 days) 10 (12 days)	1 (8 days)	1 (48 days)
5	M	53	6	++	10	—	1
6	F	38	¾	++	5	1	—
*7	F	36	2½	+++	5 (30 days) 10 (11 days)	—	1
†8	F	32	⅓	+	5	—	1
9	M	41	3	++	10	—	1
‡10	M	27	2	+++	5 (43 days) 10 (25 days)	—	1
11	F	62	15	++++	5	1 (15 days)	1 (6 days)
12	F	47	1½	+++	5 (31 days) 10 (14 days)	—	1
13	F	24	¼	+	10	—	1
14	F	62	6½	+++	5	1	—
§15	M	38	2½	++	5 (44 days)	—	1
16	F	36	1	++	5	—	1
**17	M	47	4	+++	5	—	1
18	M	51	3½	+	5 (32 days) 10 (31 days)	—	1
††19	F	39	7	+++	10 (52 days)	—	1
20	F	41	2	++	5	1	—
21	M	35	½	+	10	—	1
22	F	49	5	+++	10	—	1

*(7) When he had improved subjectively, the patient was given control injections; the persistence of the subjective improvement confirms its psychogenic nature.
†(8) On discontinuing treatment, the patient stopped growing worse.
‡(10) The patient grew worse when treated with the placebo and began to improve again when DOCA injections were resumed.

(the psychogenic nature of this improvement being confirmed by its persistence with placebo injections), and the third (Case 19), though improved both objectively and subjectively, also maintained the improvement with placebo therapy. This seems to support the view that any improvement was due not to the treatment, but to a spontaneous remission. The four remaining patients grew worse during the treatment; two of them both objectively and subjectively, and the other two only subjectively. In the two latter, the deterioration may have been psychogenic, but of the other two, one (Case 17) continued to become worse, and in the other (Case 8) the deterioration was arrested after the treatment was discontinued.

The blood pressure was maintained at about the same level during treatment in eighteen patients; the remaining four had slight increases (maximum 3 mm. Hg in one case), but all four returned to pre-treatment levels shortly after the DOCA therapy was discontinued.

Oedema appeared in three patients, in two in the ankles, in the other in the

TWO PATIENTS WITH RHEUMATOID ARTHRITIS, TREATED ACETATE AND ASCORBIC ACID

Placebo Injection	Duration of Treatment (days)	Clinical Result		Sedimentation Rate (mm./hr.)	
		Objective	Subjective	Before starting treatment	Upon discontinuing treatment
—	23	no change	no change	26	22
—	38	no change	no change	43	33
—	34	no change	no change	54	55
—	56	no change	worse	48	30
—	43	no change	no change	36	28
—	74	no change	no change	28	24
1 (21 days)	62	no change	better	64	52
—	25	worse	worse	20	20
—	29	no change	no change	42	33
1 (18 days)	86	better	better	63	45
—	21	no change	no change	29	20
—	45	no change	no change	74	36
—	52	no change	worse	43	32
—	47	no change	no change	58	50
1 (14 days)	58	no change	better	40	26
—	12	no change	no change	39	35
—	49	worse	worse	68	70
—	63	no change	no change	31	18
1 (19 days)	71	better	better	74	60
—	33	no change	no change	42	36
—	48	no change	no change	36	26
—	72	no change	no change	62	44

§(15) After six days of subjective improvement, the patient was given control injections, and the improvement was maintained. Same deductions as Case 7.

**(17) The patient continued to grow worse after treatment was discontinued.

††(19) On the second day of improvement, DOCA was replaced by placebo injections, yet the subjective and objective improvement persisted. Therefore, in this case, apart from the psychogenic factor, it seems that a spontaneous remission occurred.

legs and lower part of the thighs. All three reverted to their previous state on ceasing the treatment.

Laboratory Findings.—A routine blood test was made weekly during the treatment. Red and white cell counts and haemoglobin remained practically unchanged. A decrease in the erythrocyte sedimentation rate was observed in most cases; in three it increased slightly or remained at the same level, and in the remaining nineteen, the fall ranged from 4 to 38 mm. This lowering of the sedimentation rate is perhaps the most outstanding of our findings, for the clinical results were discouraging.

Discussion

Lewin and Wassén (1949) first reported a complete success in nine cases. Le Vay and Loxton (1949) confirmed their results, first in 23 patients of which 21 improved and later in eighty cases. Fox (1949) treated ten patients with 100 per cent. success.

Douthwaite (1949), among five patients, obtained four encouraging results. Robertson (1950) in nine cases had one dramatic response and a great improvement in all the rest. Landsberg (1950) treated nine cases with excellent results, and Nashat (1950) four with apparently good results. Hartfall and Harris (1949), however, reported contradictory findings in seventeen patients, inasmuch as four grew worse, one improved very much, and the rest improved slightly. Other authors report no effect at all; Kellgren (1949) only obtained a doubtful response in six cases, Spies and others (1949) treated six patients with six failures, and Hart and Starer (1949) achieved no good effects at all in five cases treated.

Brownlee (1950), using rats for experimental purposes, has tried to explain the actual procedure of this method; he thinks that the combination of desoxycorticosterone acetate and ascorbic acid constitutes a valuable substitute in the absence of the adrenal-cortex hormones, among which may be included a steroid of anti-arthritic effect. He points out that the secret of the production of adequate biochemical alterations lies in the union of the two substances which may be the components of an important enzymatic system, or else that the desoxycorticosterone acetate must first be reduced by the vitamin C.

On the other hand, Le Vay and Loxton (1949, 1950) believe that the desoxycorticosterone and the ascorbic acid act peripherally and not through the adrenal cortex or any other internal organ. They support this theory by noting the quick response obtained after giving the injections. The clinical findings in ten patients with rheumatoid arthritis, in whom they conducted a special study, led them to assert that the interaction between the desoxycorticosterone and ascorbic acid confined in the peripheral tissues is capable of producing all the clinical changes observed in the joints. Another theory regarding the action of DOCA and vitamin C suggests that the change is caused by oxidation of the desoxycorticosterone acetate, a chemical process which would be accomplished through the adrenal cortex.

Thus even the mechanism whereby these drugs act is variously explained by several research workers who report similar results obtained by the same method. In view of the disparity of results, some authors try to explain the failures of others by saying that the negative results are due to the small but typical responses not having been noticed; that the variation in the response depends on the momentary condition of the gland and of the physico-chemical aptitude of its cells; and, finally, that the response is sometimes delayed.

From our own observations we conclude that failure could not have been due to the causes described above, since we strictly supervised each change that could take place, and observed that, in the great majority of our patients, it did not take place in 5 minutes, nor in 2, 6, or 24 hours, nor when the treatment was discontinued. We therefore believe that the contradictory results of different workers are to be explained by one of the following causes:

(1) *Wrong Diagnosis.*—It is possible that some cases reported as having responded dramatically to this treatment, were not true cases of rheumatoid arthritis; thus it may have happened that these incorrectly diagnosed patients either actually responded, or had a spontaneous remission in the normal course of their disease.

(2) *Wrong Interpretation of Results.*—The response to a treatment must be judged both objectively and subjectively. The objective findings (perimeter of swollen joint, angle of joint motion, etc.) can be measured exactly in most cases before and after treatment. Unless this is done, there is a risk of inaccuracy in interpreting results.

(3) *Psychogenic Factors.*—The great influence of psychogenic factors is well known, especially when patients are being treated by a new method. To evaluate the results properly, therefore, these should be taken into account, using adequate controls.

(4) *Autosuggestion.*—The physician must be careful to lay aside any tendency to self-suggestion when interpreting results, this factor being of greater importance when no proper measures have been taken to avoid the first three errors.

Our results lead to the conclusion that this method of treatment is not of practical use, since, of 22 patients treated, only one actually improved and even this improvement was no more than may be expected from any other " classic " treatment. On the other hand, it is evident that if we had treated 22 patients with gold salts, physiotherapy, etc., the percentage of improvements would have been much greater.

The only remarkable fact in the series of results was the decrease of the sedimentation rate in the majority of cases, which was in sharp contrast to the clinical evolution (see Figure).

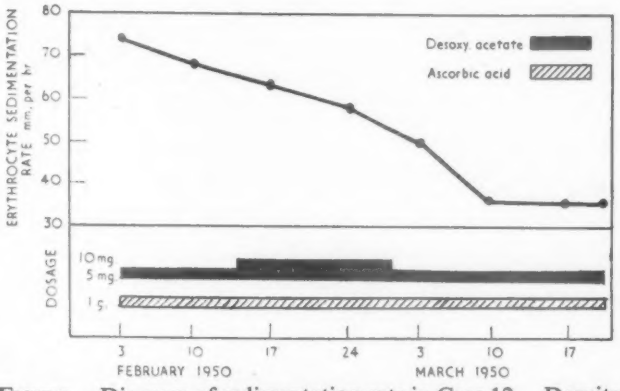

FIGURE.—Diagram of sedimentation rate in Case 12. Despite the decrease in the sedimentation rate, no clinical improvement, objective or subjective, was observed.

There are authors who compare the results obtained in rheumatoid arthritis by desoxycorticosterone acetate and ascorbic acid, with those obtained by cortisone or ACTH. We, who have treated many rheumatoid arthritis patients with these last two drugs, can assert categorically that the dramatic improvement produced by cortisone or ACTH, has not been observed with DOCA and vitamin C, nor with any other product which has so far appeared.

Summary

Twenty-two patients with rheumatoid arthritis were treated with combined injections of desoxycorticosterone acetate (DOCA) and vitamin C. Clinically, fourteen patients did not experience any change, four grew worse, and of the four that apparently improved, only one actually did so, and that only slightly. The one remarkable fact observed, was the decrease of the sedimentation rate in the majority of the cases. Results obtained by other authors are commented upon, and attempts made to explain the disagreement between previous reports.

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L'acétate de Desoxycorticostérone (DOCA) et la Vitamine C dans l'Arthrite Rhumatismale

Résumé

Vingt-deux malades atteints d'arthrite rhumatismale furent traités par des injections combinées d'acétate de desoxycorticostérone et de vitamine C. Du point de vue clinique, quatorze d'eux ne sentirent aucune différence et quatre furent plus mal; il y eut une amélioration chez quatre autres malades, mais elle ne fut qu'apparente chez trois d'eux et très légère chez le quatrième.

Un seul effet remarquable fut observé: la diminution de la vitesse de la sédimentation globulaire dans la plupart des cas. L'auteur commente sur les rapports anterieurs à ce sujet et apporte des raisons tendant à expliquer les resultats contradictoires y contenus.

El Acetato de Desoxicorticosterona (DOCA) y la Vitamina C en la Artritis Reumatoide

Resumen

Veintidós enfermos con artritis reumatoide fueron tratados con inyecciones combinadas de acetato de desoxicorticosterona (DOCA) y de vitamina C. Clinícamente, catorce enfermos no experimentaron cambio alguno, cuatro empeoraron y cuatro otros manifestaron mejoría que no fué más que aparente en tres y ligera en el cuarto caso.

Se ha observado un solo hecho notable: la diminición de la velocidad de la eritrosedimentación en la mayoría de los casos. Se comenta sobre los resultados obtenidos por otros autores y se trata de explicar la discrepancia entre los relatos anteriores.

ARTHRITIS IN RATS PRODUCED BY PLEURO-PNEUMONIA-LIKE ORGANISMS

BY

M. W. PARKES and FRED WRIGLEY*

WITH THE TECHNICAL ASSISTANCE OF MISS B. O'BRIEN

Attempts to produce in animals conditions resembling various rheumatic diseases have been numerous and have employed a wide variety of agents. Such work has usually had as its object the investigation of the part played by a certain factor in the causation of rheumatic conditions or the provision of animal subjects to test the efficacy of therapeutic agents. The work reported here was undertaken with the latter object in view.

The agent selected was a strain of pleuro-pneumonia-like organism (PPLO). This group has been surveyed by Sabin (1941) and Dienes (1945) who deal particularly with their morphology and characterization. There seems to be no evidence for associating rheumatoid arthritis with PPLO infection; attempts to isolate the organism from cases of rheumatoid arthritis have been unsuccessful (Preston, 1942). However, PPLO has been isolated from spontaneously occurring polyarthritis in rats; injection of this material into rats has been said to produce progressive changes of an arthritic nature in the joints. (Cf. also Collier and Staverman, 1940.)

Work with this organism, in rats and mice, has been reviewed by Findlay (1946). Detailed comparisons of a number of strains of PPLO isolated from animals have been made by Klieneberger (1938, 1940). One such strain, designated "L_4", is characterized by the production of abscesses, adenitis, and arthritis; this strain has been serologically identified with those employed by earlier workers on experimental arthritis in rats using PPLO. Tripi and Kuzell (1947, 1949) used a known L_4 strain of PPLO to produce experimental arthritis in rats.

Sabin (1939, 1940) and Preston (1942) describe pathological changes occurring in the joints of experimental animals injected with cultures of PPLO. Sabin regards the condition produced in mice as resembling human rheumatoid arthritis in its clinical course and pathology, but Preston (1942) finds that the changes occurring in rats more closely resemble pyogenic joint infections in man.

Experimental Procedure

A strain of PPLO (L_4) was used which was said to be capable of producing arthritis in rats. The organisms were cultured in the medium described by Edward (1947) and subcultures were made at intervals of 7 or 14 days. Thallium acetate was included as a

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bacteriostatic in cultures of isolated material, but in material for injection it was omitted. Cultural details of this organism are described by Edward (1950).

For the purposes of this work it was decided to inject, directly into the blood stream, 0·5 ml. of a subculture, in semi-solid medium, of 48-hours' incubation. The route most frequently used was intravenous, although the intracardial route was occasionally employed. The animals used throughout were male Wistar rats of about 150 g. weight.

Results

The most common sequel to injection by either route was swelling of the hind feet, usually of the plantar surface, occasionally accompanied by redness and tenderness. The swelling was often transitory and showed a tendency to subside and reappear at intervals. Less commonly the swelling involved the region of the ankle joints. The forepaws were very rarely affected. In many cases swellings were first observed 3 to 5 days after injection, which agrees with the period reported by Preston (1942), although the first appearance was often delayed beyond this.

Injected animals frequently showed subsequent loss of weight and in some cases a lowered body temperature and general depression, usually followed by death. Other symptoms, observed more rarely, included swollen testes, and conjunctivitis, both of which have been described by Tripi and Kuzell (1947) as resulting from injection of rats with PPLO. The only abnormalities of any significance observed on *post-mortem* examination were abscesses. These developed in a number of animals, most frequently in the lungs, which were often extensively involved even in animals appearing quite healthy until they were killed. Abscesses were found more often after intracardial injection than after intravenous injection. From all these abscesses PPLO could be isolated, usually in pure culture. Frequently, necrotic areas developed on the tail at or near the site of injection. An abscess was occasionally found in association with such a necrotic area, and, from such abscesses also, PPLO could be isolated. It was not found possible to isolate PPLO from any other site in infected rats, even from hearts which showed histological changes (*vide infra*). Culture of swollen joints has not resulted in recognizable colonies of PPLO. However, the tarsal and metatarsal regions of the limbs of two rats showing swellings of the plantar surface were skinned and ground in saline and the filtrate injected into the plantar region of the right foot in six rats. All developed swellings in both feet and showed pathological changes of the joints and slight changes in the heart muscle, similar to those following injection of PPLO culture.

A study of the data collected shows that several tendencies appear to characterize the behaviour of cultures of PPLO in their pathogenicity towards the rat. Progressive subculturing *in vitro* tends to reduce pathogenicity; abscesses were not produced after injection of material subcultured more than eighteen times, and the power of producing limb swellings and histological changes was also reduced after more than 33 subcultures. Tripi and Kuzell (1947) describe changes in pathogenicity with repeated subculture, which they term "passage", stating that 28 stages were necessary to produce joint swellings without peritonitis, following intraperitoneal injection. We found that animal passage increased the pathogenicity thus allowing maintenance of active cultures of the strain. The severity of the histological changes increased with repeated passage, an effect which, however, disappears with further subculture *in vitro*. Such an effect has been described by Preston (1942).

We attempted to preserve material with a known degree of pathogenicity by

freeze-drying. However, there is a tendency for such freeze-dried material gradually to lose the power of producing cultures capable of causing limb swellings.

Histological Changes

The joints and hearts of rats killed 14 to 21 days after injection were examined.

Joints.—In 64 out of 96 animals, inflammatory changes, mostly of a purulent nature, were found in the peri-articular structures. Changes of the joint surfaces, the synovial membrane, and the synovial fluid were also observed in some cases. Other changes included haemorrhage into the marrow and, in severe cases, dissolution of the articular cartilage. The infiltrating cells included large numbers of histiocytes (macrophages) and neutrophils; some lymphocytes and plasma cells were also seen. In addition multinuclear giant cells were seen in one case near necrosing bone and cartilage. Examination of two severely affected joints suggested that a mass of exudate had lodged between the articular surfaces and had become heavily infiltrated with round cells and neutrophils. This was accompanied by extensive fibrosis which had united the infiltrated mass with the surrounding tissues. There was breakdown of the cartilage matrix on one of the joint surfaces and this had permitted masses of infiltrating cells to penetrate through the head of the bone into the marrow (Figure).

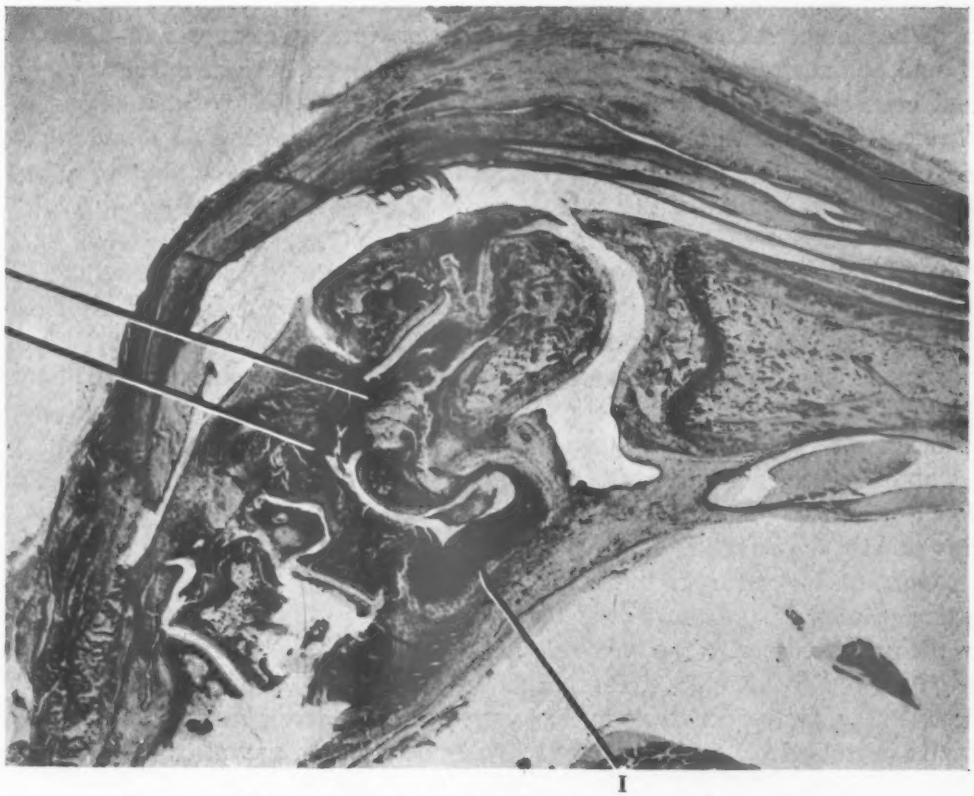

FIGURE.—Section of ankle joint of rat showing areas of inflammation.
I. Regions showing marked inflammatory action.

Hearts.—The PPLO strain used in this work appeared not only to have a predilection for joints but also caused histological changes in the hearts in more than two-thirds of the animals used.

Out of 96 animals, 58 showed some degrees of change in the myocardium, mostly of an inflammatory nature, and characterized by the presence of cells of the types described as associated with the joint lesions.

Discussion

These studies were undertaken to produce a method for screening substances for use in the treatment of the rheumatic diseases. Kuzell and others (1949) claimed to have screened a number of substances by inducing arthritis with an L_4 strain of PPLO. The course of the disease is favourably altered by gold salts and aureomycin compares well with these substances when given in the food or parenterally; salazopyrin and cupralene exerted some beneficial effect. Sodium gentisate and cinchophen were ineffective. Kuzell and Mankle (1950) reported that terramycin had a favourable effect on the course of the disease, but that cortisone had none.

We felt that a combination of clinical and histological evaluation might enable us to draw conclusions as to which of the many manifestations of rheumatic disease our condition resembled and also to be more certain of the results of our injections.

When abscesses appeared, we decided that further passage and subculture should be undertaken in the hope that, when the more obvious infective element had been eliminated, we should be able to produce at will joint swellings of a rheumatoid type with some of the histological changes described as found in man.

We have not seen the round-cell focus in skeletal muscle described by Gibson (1948), the infiltration in our specimens being always of a diffuse nature. The changes in the synovium were also more diffuse than those of the Allison-Ghormley type. There was no close correlation between the occurrence of swelling and histological findings. A number of swollen feet showed no detectable abnormalities, and on histological examination changes were found to have taken place in joints of some limbs which had appeared normal throughout the period of observation.

Preston (1942) stated that the joint lesions of rats which have been injected intracardially with PPLO are purulent in nature. The inflammation leads to an abscess involving all structures of the joint. Sabin and Warren (1940) state that a similarly induced arthritis in mice is primarily proliferative in nature, and in this respect shows some similarity to rheumatoid arthritis.

Our results lead us to agree that the primary inflammatory reaction is peri-articular in nature, as shown to a greater or lesser extent by the joints of two-thirds of the rats examined. The type of lesion produced in rats by this particular strain of PPLO rather resembles that produced by Preston (1942). The frank abscesses, described by him as occurring in the joints, were not found, but the changes in the hearts resembled the purulent heart lesion he describes in the rat.

Conclusions

The histological picture in the rheumatic diseases differs in considerable detail from that found in our experimental animals, and we cannot conclude, therefore, that arthritis produced by PPLO in rats consistently resembles any one

of the rheumatic diseases. This would not matter from the point of screening new compounds if it could be shown that any of the substances known to be useful in rheumatism therapy could prevent or influence the course of the condition, but as the arthritis we produced tended to spontaneous resolution, we do not feel that it can be used as a valid screening test.

Summary

Experiments in the production of arthritis in rats by the injection of pleuro-pneumonia-like organisms, histological and clinical findings, and the effect of passage and subculture on the pathogenicity of the organisms are described.

No close correlation was found between clinical appearance and histological changes, and the disease tended to spontaneous resolution. It is therefore concluded that the method cannot be used as a valid screening test for substances thought to be useful in the treatment of the rheumatic diseases.

We are greatly indebted to Dr. D. G. ff. Edward of the Wellcome Veterinary Station, who kindly provided the strain of PPLO used in this study, and to Dr. G. H. Bourne of the London Hospital Medical School, who did the histological examinations.

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Arthrite produite chez les Rats par des Organismes du Type Pleuro-pneumonique

RÉSUMÉ

Les auteurs rapportent leurs expériences qui consistaient à provoquer l'arthrite chez les rats par des injections d'organismes du type pleuro-pneumonique. Ils décrivent les résultats histologiques et cliniques ainsi que les effets de passage et d'atténuation en culture sur le pouvoir pathogène des germes.

Ils n'ont pas trouvé de rapport entre l'aspect clinique et les altérations histologiques; la maladie tendait à la guérison spontanée. Ils en concluent que cette méthode n'a guère de valeur pour essayer des substances qu'on croit utiles dans le traitement de l'arthrite rhumatismale.

Artritis producida en Ratas por Organismos del Tipo Pleuro-pneumónico

RESUMEN

Los autores relatan sus experimentos en la producción de artritis en ratas mediante inyecciones de organismos del tipo pleuro-pneumónico. Describen los resultados histológicos y clínicos así como los efectos de pasaje y de atenuación en cultivo sobre el poder patógeno de los gérmenes.

No pudieron establecer correlación entre la apariencia clínica y los cambios histológicos; la enfermedad mostró tendencia de terminarse espontáneamente. Concluyen que este método no puede ser usado como prueba válida para substancias que se cree útiles para el tratamiento de las enfermedades reumáticas.

THYMOL REACTION IN RHEUMATOID ARTHRITIS*

BY

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New methods of examination in the study of rheumatoid arthritis, including the streptococcus agglutination test, the differential agglutination reaction with sensitized sheep corpuscles, determination of the antihyaluronidase inhibitor in serum, electrophoretic analysis of the serum proteins, and determination of 17-ketosteroids and glucocorticoids in the urine, yield characteristic findings and fit naturally into the symptomatic mosaic of this clinical entity.

The thymol reaction was first elaborated for practical use in 1944 by Maclagan, and it has since been employed in the diagnostic and prognostic estimation of various diseases of the liver, especially epidemic hepatitis. The prevailing view is that the reaction is due to certain changes in the gamma globulin, though some authors assert that it should rather be attributed to changes in the serum lipoproteins.

A positive thymol reaction in rheumatoid arthritis has been reported previously by Carter and Maclagan (1946), Stillerman (1948), and Poulsen (1949). Stillerman found the reaction positive in 82 per cent. of cases, but Carter and Maclagan did so in only 38 per cent., whereas the colloidal gold test gave a positive reaction in 76 per cent. of their material.

One purpose of the present investigation was to ascertain whether any definite relationship existed between the thymol reaction and the streptococcus agglutination reaction, chiefly because this sero-reaction, which is positive in about 70 to 80 per cent. of cases of rheumatoid arthritis, is also explained by most investigators as attributable to changes in the serum globulins.

Material

The present studies comprised 21 patients with typical rather severe rheumatoid arthritis, more than half having been troubled with rheumatic disease for more than 10 years. The control material consisted of patients from the same department, suffering from various medical diseases, mainly chronic in character but not including liver lesions. The average age of the patients in the two groups was about the same (60 years).

Method

The thymol is added to a serum under particular conditions, and a precipitate, consisting of thymol-serum-lipoid, appears. The degree of precipitation is read directly

* Aided by a grant from the National Danish Association Against Rheumatic Diseases.

in a photometer, and recorded in decimals. Values under 0·15 are considered normal, but values over 0·15 are considered decidedly pathological.*

Results

(1) **Control Material.**—In 31 patients with various medical lesions the thymol test gave the following results:

Normal values (0-0·15) in 29 patients (93 per cent.).
Increased values (≧0·15) in 2 patients (7 per cent.).

(2) **Patients with Rheumatoid Arthritis.**—The results of the thymol test in 21 patients were distributed as follows:

Normal values (0-0·15) in 5 patients (24 per cent.).
Increased values (≧0·15) in 16 patients (76 per cent.).

Thus a pathological increase in the value for the thymol reaction occurred about ten times more frequently among the patients with rheumatoid arthritis than in the control material.

The results of the streptococcus agglutination tests were distributed in the 21 rheumatoid-arthritic patients as follows:

Negative streptococcus agglutination in 6 patients (29 per cent.).
Positive streptococcus agglutination in 15 patients (71 per cent.).

This is quite in keeping with the findings reported previously by Goldie (1938), 75 per cent.; Cecil and deGara (1946), 60 per cent.; Edström and Winblad (1947), 76 per cent.; and Kalbak (1948), 77 per cent.

These results are all set out in Table I:

TABLE I

THYMOL TEST AND STREPTOCOCCUS AGGLUTINATION TEST IN 21 CASES OF RHEUMATOID ARTHRITIS

Case No.	Sex	Age	Thymol Test		Streptococcus Agglutination Test		Duration of Illness (years)	Activity of Disease
			Reading	+/0	Titre	+/0		
1	F	32	0·18	+	1 : 40	+	9	+
2	F	40	0·11	0	1 : 80	+	3	++
3	F	54	0·22	+	1 : 40	+	1	+++
4	M	59	0·33	+	1 : 80	+	10	+++
5	M	63	0·26	+	1 : 320	+	6	+++
6	M	52	0·22	+	1 : 160	+	8	+++
7	F	71	0·67	+	1 : 80	+	7	+++
8	F	40	0·18	+	0	0	17	++
9	F	54	0·24	+	1 : 160	+	23	+++
10	M	52	0·25	+	1 : 160	+	11	+++
11	F	58	0·26	+	1 : 80	+	19	+++
12	F	54	0·10	0	0	0	30	++
13	F	53	0·11	0	0	0	15	++
14	M	56	0·25	+	1 : 160	+	14	+++
15	F	49	0·25	+	1 : 80	+	13	+++
16	F	69	0·06	0	0	0	4	++
17	F	15	0·08	0	1 : 160	+	1	+++
18	F	73	0·23	+	1 : 320	+	14	++++
19	F	57	0·16	+	0	0	1	++
20	F	20	0·16	+	0	0	6	++
21	M	59	0·41	+	1 : 160	+	19	++

* The thymol reactions were performed by the Medicinsk Laboratorium, Copenhagen.

A comparison of the outcome of the thymol reaction with that of the streptococcus agglutination test may be tabulated as follows:

TABLE II

Thymol Reaction		Positive (16)	Negative (5)
Streptococcus Agglutination Test ..	Negative (6)	3	3
	Positive (15)	13	2

Thus it will be noticed that a positive thymol reaction occurs more frequently in the group having a positive streptococcus agglutination reaction—which was to be expected if both reactions are expressions of changes in the serum globulin concentration.

A comparison of the outcome of the thymol reaction with the degree of activity of the joint disease* may be tabulated as follows:

TABLE III

Thymol Reaction	Activity of Joint Disease				Total Cases
	+	++	+++	++++	
0-0·15	—	4	1	0	5
≧0·15	—	5	10	1	16
Total	—	9	11	1	21

It thus appears highly probable that a positive thymol test is more likely to occur in patients whose joint disease is at a more active stage.

In keeping with previous investigations, a positive thymol reaction has been demonstrated in about 75 per cent. of the patients with rheumatoid arthritis. Furthermore, this reaction is found to be positive more often when the disease is at a more active stage. The incidence of positive thymol reactions and positive streptococcus agglutination reactions runs fairly parallel, which favours the hypothesis that the two reactions are both attributed to the changes in the serum proteins. Sufficiently detailed studies have not yet been carried out on the behaviour of the thymol reaction in rheumatoid arthritis for any appraisal of its diagnostic and prognostic value in this disease, but it can already be established that a positive thymol reaction fits very well into the mosaic of biochemical reactions characterizing the picture of advanced rheumatoid arthritis.

Summary

The thymol reaction in 21 patients suffering from rheumatoid arthritis was found to be positive in about 75 per cent. The incidence of positive thymol reactions is similar to the incidence of positive streptococcus agglutination reactions.

* According to the standards set up by the American Rheumatism Association (1949).

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Réaction du Thymol dans l'Arthrite Rhumatismale

RÉSUMÉ

Sur 21 malades atteints d'arthrite rhumatismale la réaction du thymol fut positive dans environ 75% des cas. La fréquence des réactions du thymol positives est similaire à celle des réactions positives d'agglutination du streptocoque.

Reacción de la Turbidez del Timol en la Artritis Reumatoide

RESUMEN

De 21 enfermos con artritis reumatoide la reacción de la turbidez del timol fué positiva en cerca de 75% de los casos. La frecuencia de las reacciones de la turbidez del timol positivas es similar a la de las reacciones positivas de aglutinación del estreptococo.

VARIATIONS IN THE THYMOL REACTION IN RHEUMATOID ARTHRITIS PATIENTS UNDER TREATMENT WITH CORTISONE AND ACTH*

BY

K. KALBAK

From the Noerre Hospital, Copenhagen

As demonstrated by various investigators (Carter and Maclagan, 1946; Stillerman, 1948; Poulsen, 1949; Kalbak, 1951), the thymol reaction is positive in rheumatoid arthritis patients at a somewhat advanced and active stage of the disease. This positive reaction is assumed to be due to changes in the serum proteins.

Patients with rheumatoid arthritis generally show marked changes in the serum proteins in the form of increased total protein, hypo-albuminaemia, and increase in α globulin and, especially, $\bar{\gamma}$ globulin. These shifts in the serum proteins follow rather closely the curve of the erythrocyte sedimentation rate, and also to some extent, the variations in the clinical state of the patient.

When rheumatoid arthritis is being treated with cortisone or ACTH decisive changes take place in the serum proteins. The hypoproteinaemia subsides, and the albumin/globulin ratio becomes normal.

In keeping with the theory that the positive thymol test is due to pathological

* Aided by grant from the National Danish Association Against Rheumatic Diseases.

changes in the serum proteins, it seemed reasonable to expect this reaction to approach normal, when the patients were treated with these hormones.

Clinical Findings

Of four patients suffering from typical rheumatoid arthritis, one was treated with cortisone, while three were given ACTH. In three of the patients the thymol reaction, which was decidedly positive before the institution of treatment, was controlled by repeated determinations, the normal limit for the thymol test being set at 0·13-0·15.*

The results are shown diagrammatically in the Figure, which also shows dosage. ACTH was given intramuscularly in small quantities, 5 to 10 mg., several times daily.

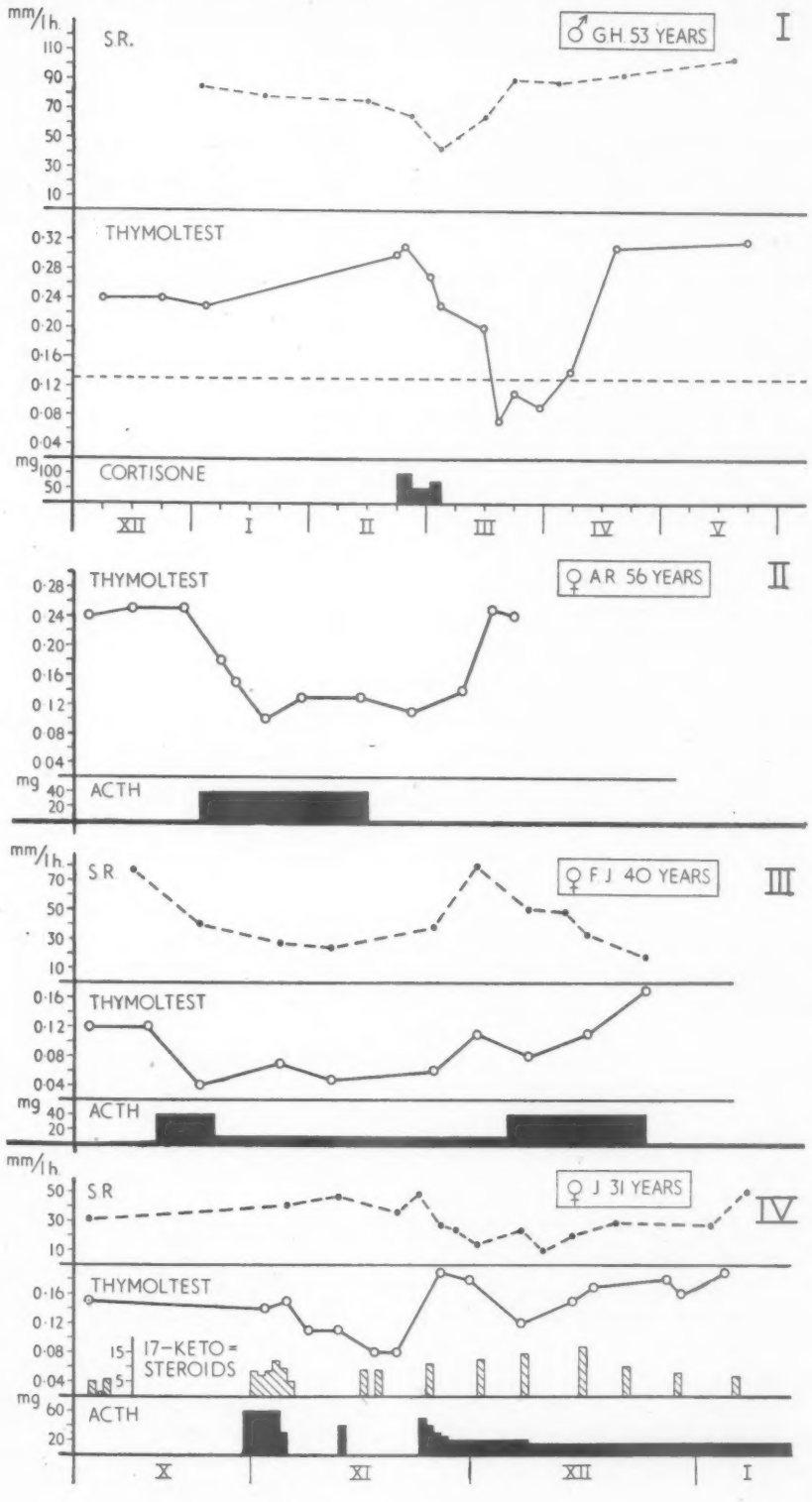
Case 1. Male, aged 53, in an advanced stage of rheumatoid arthritis.
Thymol reaction repeatedly strongly positive (0·24).
Erythrocyte sedimentation rate about 80 mm. in 1 hour.
Cortisone acetate† was given for 10 days (altogether 750 mg.); this treatment had an excellent clinical effect, and the thymol reaction at once showed a tendency to fall, and minimum values (about 0·08) were obtained for about 2 weeks after discontinuing the treatment. After this, the thymol reaction increased again to an even higher level (about 0·32) than before. This was in keeping with the aggravation of the clinical state of the patient, as well as with a rise in the erythrocyte sedimentation rate to about 100 mm. in 1 hour. The thymol reaction and erythrocyte sedimentation rate ran parallel.

Case 2. Female, aged 56, confined to bed with severe rheumatoid arthritis.
Thymol reaction distinctly positive (0·25).
ACTH‡ therapy (40 mg. daily for 30 days) had only a moderate clinical effect, whereas the thymol reaction decreased to a normal level (about 0·12). Two weeks after discontinuing treatment the thymol reaction had risen to the initial level (about 0·25).

Case 3. Female, aged 40, with moderately severe rheumatoid arthritis.
Thymol reaction before treatment, normal (0·12).
During treatment with ACTH, which was given for about two months, the level of the thymol reaction decreased. At the beginning and towards the end of the course ACTH was given in fairly large doses (40 mg. daily), and in the intervening longer period the daily dose was only 10 mg. In spite of a relatively small dosage of ACTH a fairly good clinical effect was maintained, except in the final period, when the decrease in the clinical effect was accompanied by an increase in the level of the thymol test—apart from a brief fall after an increase in the dosage of the hormone. On the whole, the outcome of the thymol test and the E.S.R. ran parallel except in the final phase, when the E.S.R. fell steadily in spite of the decrease in clinical effect and increasing thymol reaction.

Case 4. Female, aged 31, with rather severe rheumatoid arthritis (Stage III).
Thymol reaction slightly increased (0·15).
Brief treatment (6 days) with moderate doses of ACTH brought about a considerable fall in the thymol values (down to 0·08). The minimum value was reached about two weeks after discontinuing the treatment and then rose at once to values above the initial level. A second course of ACTH produced a further fall in the thymol reaction, but when small doses of the hormone were given throughout a considerable period, the thymol values again increased, being accompanied by a fairly parallel rise in the erythrocyte sedimentation rate. The output of 17-ketosteroids, which was increasing under the hormone

* The thymol tests were performed by Medicinsk Laboratorium, Copenhagen.
† Cortisone was kindly furnished for experimental purposes by Merck & Co., U.S.A.
‡ ACTH (RMC) was kindly furnished by the Roskilde Medical Company, Denmark.


mm/1h.
S.R.
♂ G.H. 53 YEARS
I
THYMOLTEST
CORTISONE
mg
XII
I
II
III
IV
V
THYMOLTEST
♀ A.R. 56 YEARS
II
ACTH
S.R.
♀ F.J. 40 YEARS
III
THYMOLTEST
ACTH
S.R.
♀ J. 31 YEARS
IV
THYMOLTEST
17-KETO-STEROIDS
ACTH
X
XI
XII
I

therapy, fell during the final phase when only small amounts of ACTH were given daily—and thymol reaction and erythroctye sedimentation rate increased.

Discussion

In the variegated multiplicity of clinical-biological, biochemical, and serological examinations, each of which contributes to our estimation of the effect of the hormonal therapy in rheumatoid arthritis, the thymol test appears to deserve consideration.

During the administration of cortisone or ACTH the thymol reaction as a rule falls sharply, but it increases again after discontinuing the treatment, most often to values higher than the initial level.

As in this disease the abnormal serum protein values become normal under hormone treatment, it seems reasonable to attribute changes in the thymol reaction to the decrease in the serum proteins, which supports the theory that an abnormally increased thymol reaction is due to changes in the serum protein.

In the cases cited above the variations of the thymol reaction matched those of the E.S.R. and of the clinical state of the patient (except in Case 3). The sedimentation test may still be regarded as the simplest and most reliable laboratory test in estimating the effect of cortisone and ACTH therapy in rheumatoid arthritis.

Summary

The thymol reaction which is normally pathologically increased in rheumatoid arthritis, becomes normal during treatment with cortisone or ACTH. This reaction may be included in the tests of the effect of these hormones.

The observations here reported support the view that a positive thymol reaction is due to changes in the serum proteins.

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Variations de la Réaction du Thymol chez les Malades atteints d'Arthrite Rhumatismale Traités par la Cortisone et par l'ACTH

Résumé

La réaction du thymol, généralement augmentée pathologiquement dans l'arthrite rhumatismale, devient normale pendant le traitement par la cortisone et par l'ACTH. Cette réaction peut donc faire partie des tests sur l'effet de ces hormones.

Les observations rapportées ici renforcent le point de vue qu'une réaction du thymol positive est due aux modifications dans les protéines sériques.

Variaciones de la Reacción de la Turbidez del Timol en los Enfermos con Artritis Reumatoide Tratados por la Cortisona y por la ACTH

Resumen

La reacción de la turbidez del timol, que suele ser patológicamente aumentada en la artritis reumatoide, se vuelve normal durante el tratamiento con cortisona o ACTH. Esta reacción puede ser incluida en las pruebas sobre el efecto de estas hormonas.

Las observaciones aquí relatadas refuerzan el punto de vista de que una reacción de la turbidez del timol positiva se debe a alteraciones en las proteinas del suero.

HEBERDEN SOCIETY

Clinical Meeting.—The Heberden Society held a meeting on April 6, 1951, at the Royal Free Hospital, London, N.W.3. The President, Sir Henry Cohen, was in the chair.

DR. ERNEST FLETCHER described the use of intra-articular cortisone in rheumatoid arthritis cases of long standing in the wards of the Royal Free Hospital.

It was thought originally that the opinion of Seifter and others (1949) that the injection of cortisone into the articular cavity diminished the permeability of the synovial membrane was probably correct, and work was begun partly on this assumption, but later experiments carried out in the Unit threw some doubt on this conclusion.

Two schemes of intra-articular dosage were used. Scheme I employed a single injection of 100 mg. cortisone, and Scheme II doses of 10 mg. six-hourly for three days.

By a photo-electric method the opinion was formed that cortisone is sparingly soluble in the synovial fluid, but the conclusions reached were not absolutely definite as a dispersing agent is added to cortisone acetate when it is issued by Merck and Company, and it may be that this interfered with the colorimetric readings. Biochemical findings were provided as a check in Scheme I, and in Scheme II comparisons were made with intramuscular cortisone.

It was concluded that the intra-articular administration of cortisone is not at present as useful as intramuscular administration. Although the site of action of cortisone is thought to be peripheral, it is probable that it acts not on the cartilage or synovial fluid but on the collagen tissue of the peri-articular structures.

DR. LISTER said that he was sure the President's suggestion that the effect of cortisone on insulin sensitivity might be of great importance was right, but so few cases had so far been investigated that it was not yet possible to draw any definite conclusions (Lister and others, 1951). It was well known that cortisone caused certain non-diabetic patients to develop glycosuria, and furthermore that in diabetic patients the disease might become more severe with cortisone therapy. He said that Dr. Ernest Fletcher suggested that as investigations into insulin sensitivity in a large group of diabetics were being made, it might be of interest to investigate the insulin sensitivity of patients treated with cortisone. The insulin sensitivity test used was that devised by Himsworth (1936); patients were given 30 gm. glucose per sq. m. body surface on one day under fasting conditions, and the effect on the blood sugar levels over the next hour was observed, then the same amount of glucose was given on another day with 5 units soluble insulin per sq. m. body surface intravenously at the same time. The way in which the insulin modified the glucose curve was taken as the index of insulin sensitivity. Six patients were investigated; three of these increased their insulin sensitivity after cortisone, and three showed a decrease in sensitivity. The findings were illustrated by the following Table.

Case	Insulin Sensitivity		Variation
	Normal Conditions	After 1 g. Cortisone or ACTH	
1	0·00	1·03 (cortisone)	insensitive to sensitive
2	0·04	0·58 (cortisone)	
3	0·99	1·48 (ACTH)	
4	0·59	0·26 (cortisone)	sensitive to insensitive
5	0·97	0·00 (cortisone)	
6	1·11	0·00 (cortisone)	

Dr. Lister said that these findings called for further investigation as the cause of the variations was not yet established.

DR. E. G. L. BYWATERS said that they were investigating the effect of intra-articular cortisone on the volume of synovial fluid and its viscosity. A certain case had effusions in both knee joints. Both effusions were aspirated, the volume was measured and the viscosity estimated. He injected cortisone into one knee and saline into the other knee. Fourteen days later he found that the volume was decreased and the viscosity increased in the knee treated with cortisone, but that these changes were not seen in the knee treated with saline. Subsequently the injections were reversed and cortisone produced the same changes in the knee into which it was injected. On a third occasion the first procedure was again followed, and cortisone again caused a decrease in the volume of synovial fluid and an increase in the viscosity. The degree of viscosity was due not to an increase in the amount of mucin, but to its polymerization. There was no systemic response even to doses up to 300 mg., as shown by the unchanged character of the fluid in the other knee.

This promoted a discussion between Dr. Bywaters, Dr. Buchan, and Mrs. David, biochemist, and Sir Henry Cohen called upon Dr. Buchan to describe recent experiments on synovial fluid.

DR. J. F. BUCHAN said that no one knew in what form mucin naturally exists in synovial fluid. It had been conclusively shown that it was responsible for the viscosity. Normal knee-joint fluid had a relative viscosity of 208 at 38° C. In all pathological effusions the viscosity was greatly reduced and the mucin degraded. This was shown by the alteration in the physical characteristics of the precipitate after the addition of acetic acid. Factors affecting the viscosity of mucin solutions were of two types:

(1) Those producing an irreversible diminution in viscosity,

(2) Those producing reversible changes, which were four in number:

(*a*) Variations in the mucin concentration,
(*b*) Variations in the temperature of the solution,
(*c*) Variations in the *p*H of the solution,
(*d*) Variations in the type and concentration of salt in the solvent.

Any of these four factors might be responsible in part for the decreased viscosity observed. Only two of the normal constituents of synovial fluid had been found capable of degrading mucin; these were ascorbic acid and alkaline phosphatase, which both produced irreversible diminution in the viscosity of mucin solutions and flakey or particulate precipitates on the addition of acetic acid. During the last nine months an effort had been made to discover which, if any, of these factors were responsible for the reduced viscosity in rheumatic diseases.

The findings so far were no more than a report on the progress of the work done

and in the four factors producing reversible changes in the viscosity of mucin solutions, no account had been taken of the type and concentration of the salt in the solution. A Table compiled by Ropes and others (1947) showed that this factor was unlikely to be an important one. In cases of rheumatoid arthritis, not treated with cortisone, ACTH, or ascorbic acid, in which the joint fluid had been examined, a significant direct relationship was found to exist between the relative viscosity, i.e. the polymerization of mucin and the synovial fluid ascorbic acid levels—the higher the ascorbic acid, the lower the viscosity. When serum ascorbic acid was plotted against synovial fluid ascorbic acid, the cases treated with vitamin C were included, and it was seen that especially in the higher values a significant relationship existed. No relationship was found between relative viscosity and *p*H total protein or mucin concentration. It was concluded from these results that part of the synovial fluid ascorbic acid was to some extent responsible for the degradation of synovial fluid mucin.

Dr. Buchan paid tribute to the work of Dr. Bauer and his colleagues in Boston, and expressed his thanks to Dr. Marion Ropes and Prof. Rimington of University College Hospital Medical School for their helpful advice in this investigation.

MR. CHARLES GRAY spoke briefly about the chronic shoulder joint lesion known as chronic peri-arthritis or "frozen shoulder", and emphasized the importance of the supraspinatus lesion in this condition. *Post-mortem* and dissecting-room examinations showed the frequency with which degenerative changes occurred in the supraspinatus tendon. This tendency to degeneration in the tendon was partly due to its anatomical situation, where it was liable to injury in falls on the outstretched arm, and to repeated micro-trauma as it came into contact with the acromion during elevation of the arm. There was also, no doubt, a constitutional factor.

Operations performed in cases of chronic peri-arthritis or frozen shoulder showed that in these cases there was always a degenerative change in the tendon, and it seemed likely that this degeneration was the principal cause of these chronic shoulder lesions.

The cases could be divided into four groups:

(1) With pain but without stiffness (tendonitis). These showed a sudden tendency to spontaneous recovery but might persist for months.
(2) With pain and stiffness. In some of these cases there was actual contracture of the shoulder besides muscle spasm, and manipulation under anaesthesia was necessary.
(3) Complete rupture of the supraspinatus tendon. This caused limitation of active abduction, although passive movements were at first full and the deltoid was contracting. The most important thing was to palpate the rupture. A gap could be felt in the tendon immediately to the outer side of the acromion process. In selected cases suture gave good results.
(4) Calcified deposits in the supraspinatus tendon. These might exist for years without causing symptoms, but might also be a source of chronic pain, and in some cases, when the deposit increased and ruptured into the sub-acromial bursa, aching pain might occur and persist for some days or weeks. There was a sudden tendency to spontaneous absorption of the deposit and operation should be reserved for these cases in which severe pain persisted in spite of rest and analgesics.

MRS. V. DAVID demonstrated the following methods of synovial fluid examination in the laboratory:

(1) Ascorbic acid by 2,6-dichlorophenol indophenol titration in metaphosphoric acid.
(2) Ascorbic acid by coupling with 2,4-dinitrophenyl hydrazine.
(3) Alkaline phosphatase by phenol liberation.
(4) Viscosity determination using the adaptation of the Ostwald viscometer described by Woodmansey and Wilson (1948).
(5) Mucin precipitation and determination by the method of Ropes and others (1947).
(6) Nitrogen determination by the micro-Kjeldahl apparatus of Markham (1942).
(7) *p*H measurement of synovial fluid.
(8) Cortisone extraction of urine by the method of Cope (1951).

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Presidential Address.—This was delivered on April 6, 1951, by Professor Sir Henry Cohen, at 41 Portland Place, London, W.1. The title was "Some Observations on the Clinical Analysis of Pain, especially in Rheumatic Disease". The speaker was introduced by the Chairman, Dr. W. S. C. Copeman, and a vote of thanks was proposed by Professor R. E. Tunbridge. A report of the address will appear in the next issue of this Journal.

EMPIRE RHEUMATISM COUNCIL

As part of the medical contribution to the Festival of Britain, an "Empire Rheumatism Council Week" for overseas medical visitors is being organized, in conjunction with the Heberden Society and the British Branch of the International League Against Rheumatism. This will take the form of a tour of rheumatism centres in England, between September 11 and September 20, 1951, to precede the Barcelona Congress.

The programme will be as follows:

Tuesday,	September	11	London.
Wednesday,	,,	12	Manchester and/or Buxton.
Thursday,	,,	13	Armours Conference (on ACTH), Harrogate.
Friday,	,,	14	
Saturday,	,,	15	Harrogate and/or Leeds.
Sunday,	,,	16	Free.
Monday,	,,	17	Bath and/or Taplow.
Tuesday,	,,	18	Bath and/or London.
Wednesday,	,,	19	London and/or Taplow.
Thursday,	,,	20	Leave London for Barcelona.

A limited number of guest lectureships will be available at the various centres referred to above.

Although Edinburgh is not included in the Tour, members of the medical profession who arrange to visit the city will be welcome to see the Rheumatic Unit at the Northern General Hospital.

Further details of the Tour may be had from the General Secretary, Empire Rheumatism Council, Tavistock House (N.), Tavistock Square, London, W.C.1. Those who propose to join the Tour should inform the General Secretary not later than July 1, 1951.

NEW YORK RHEUMATISM ASSOCIATION

The Annual Meeting of the New York Rheumatism Association was held at the Cornell University Medical College on April 11, 1951. Dr. Cornelius H. Traeger presided, and the following papers were given:

Adrenal Function and Steroid Excretion in Disease. By K. Dobriner, S. Lieberman, H. Wilson, M. Dunham, and I. Somerville of the Sloan Kettering Institute and Memorial Hospital, N.Y.

Hypercoagulability of the Blood Associated with ACTH and Cortisone. By S. W. Cosgriff of the College of Physicians and Surgeons, Columbia University.

Structural Changes in the Adrenal Gland Following ACTH and Cortisone Therapy. By L. Sokoloff, J. T. Sharp, and E. H. Kaufman of the New York University College of Medicine.

Further Observations on Long-Term Effects of Cortisone in Patients with Rheumatoid Arthritis. By R. H. Freyberg, C. H. Traeger, W. Squires, M. Patterson, and C. Stevenson of the Hospital for Special Surgery, N.Y.

Preliminary Report on the Combined Use of Hormonal and Gold Therapy in the Treatment of Rheumatoid Arthritis. By W. H. Kammerer, R. L. Cecil, and W. T. Robbins of the Cornell University Medical College.

Degenerative Joint Disease of the Hip (Malum Coxae Senile, Osteo-Arthritis of the Hip): Relief of Symptoms Following Cortisone Therapy. By R. H. Boots, L. C. Yen, K. J. McMorrow, and C. Ragan of the College of Physicians and Surgeons, Columbia University.

ACTH and Cortisone in Periarthritis of the Shoulder (" Frozen Shoulder "). By S. Berkowitz, M: Ehrlich, M. Silver, and O. Steinbrocker of the Arthritis Clinics of the Hospital for Joint Diseases and Lenox Hill Hospital, N.Y.

The Effect of Post-Partum Plasma in Rheumatoid Arthritis. By L. Granirer of the Arthritis Clinic, Queens General Hospital, N.Y.

The following were elected to be officers of the N.Y.R.A. for the coming year:

President:	Currier McEwen.
Vice-President:	Charles Ragan.
Secretary-Treasurer:	Robert M. Lintz.

The following were elected for a three-year term on the Executive Committee:

Joseph J. Bunim.
Robert L. Preston.

BRITISH BRANCH OF THE EUROPEAN LEAGUE AGAINST RHEUMATISM

The Annual General Meeting will be held at the Arthur Stanley Institute (Middlesex Hospital), Peto Place, London, N.W.1, at 2 p.m. on July 6, 1951. This was followed by a Medical Meeting at which short papers were presented by Drs. Bernard Schlesinger, L. J. Barford, G. D. Kersley, and others.

DANISH NATIONAL ASSOCIATION AGAINST RHEUMATIC DISEASES

ANNUAL REPORT, 1949-50

The activities of the Association during the past year have included subsidizing the treatment of needy patients at three selected sanatoria. A large sum was allocated for research into the effect of cortisone in certain of the rheumatic diseases, and an agreement has been made with the commercial interests involved, whereby ACTH is being produced in Denmark in increasing quantities. The President of the Association, Professor E. Jarløv, was elected President of the Ligue Internationale contre la Rhumatisme.

It would be pleasant to be able to record that every civilized country had an equally active and enlightened rheumatic organization at work. W. S. C. C.

CORRESPONDENCE

IRON THERAPY IN THE ANAEMIA OF RHEUMATOID ARTHRITIS

To the Editors, *Annals of the Rheumatic Diseases.* 6.6.51.

SIRS,

In these days of ultra-scientific medicine, published work contains so much biochemical and mathematical data that the busy clinician may be tempted to seek information exclusively from the pages of your distinguished contemporary *Readers' Digest.* Fortunately, in an effort to keep medical journals readable, there is a slowly growing tendency for the writer to exclude from his reports all inessential matter—however much the inclusion of this might appear to increase his intellectual stature and halo of erudition. But this tendency does not imply that the investigator no longer recognizes the need to check the validity of his results: he will do so, in any event, for his personal satisfaction, before considering any phase of his enquiry to be complete.

Accordingly, before submitting to you my recent report on "Oral and Intravenous Iron Therapy in the Anaemia of Rheumatoid Arthritis"*, I passed my results to colleagues in the Department of Economics of the University of Leeds, for statistical examination: in reply, I received a comprehensive analysis which, you may agree, although satisfying

* *Ann. rheum. Dis.* (1950). **9**, 358, and (1951). **10**, 86.

was too long to incorporate in a brief paper. I therefore chose to describe the results as statistically significant, instead of giving a series of mathematical expressions which might have gratified the occasional enthusiast like Dr. Bywaters, but would have been somewhat indigestible for the "average reader"—if one may use such an imprecise phrase.

Yours, etc.,

D. N. Ross.

Royal Bath Hospital, Harrogate.

STATISTICAL SUPPLEMENT

by D. N. Ross

The data can best be summarized as follows:

If y is the result after treatment, x is the result before treatment, then

$$\left.\begin{aligned} \text{for Group } P \quad y &= 45{\cdot}60 + 0{\cdot}477x \\ \text{for Group } V \quad y &= 60{\cdot}92 + 0{\cdot}333x \end{aligned}\right\} \quad (1)$$

These relations can also be written,

$$\left.\begin{aligned} P, \ (y - 87{\cdot}2) &= (0{\cdot}477)\ (x - 87{\cdot}2) \\ V, \ (y - 91{\cdot}3) &= (0{\cdot}333)\ (x - 91{\cdot}3) \end{aligned}\right\} \quad (2)$$

These can be interpreted as showing that in both cases the treatment has a tendency to bring the patient nearer to a normal level of 90 approximately.

The difference between the slopes of the two relations (1) are not significant.

There is also a difference in the variances of the results of the two groups both before and after treatment, giving some indication that the results of treatment given to Group V are less predictable or Group V is less homogeneous than Group P. These differences are, however, not significant.

Taking these results into account, the relationships (1) can alternatively be written:

$$\left.\begin{aligned} P \pm y &= 50{\cdot}7 + 0{\cdot}40x \pm 7{\cdot}6 \\ V \pm y &= 56{\cdot}3 + 0{\cdot}40x \pm 7{\cdot}6 \end{aligned}\right\} \quad (3)$$

The difference of 5·6 points is a measure of the difference in the efficacy of treatment in the two groups and is significant at the 1 per cent. significance level.

An alternative formulation corresponding to equation (2) would be to assume that both treatments have the same normal level 90. This leads to

$$\begin{aligned} P \ (y - x) &= 0{\cdot}42\ (90 - x) \\ V \ (y - x) &= 0{\cdot}71\ (90 - x) \end{aligned}$$

This could be interpreted to mean that the treatment applied to V is some 70 per cent. more effective than that applied to P. The difference is again statistically significant at the 1 per cent. level.

BOOK REVIEWS

Annotated Bibliography of Cortisone, ACTH, and Related Hormonal Substances. Published quarterly by the Cortisone Committee of the Empire Rheumatism Council. First Quarter, 1951. 5*s*.

The second issue of this publication covers the literature which has appeared up to November, 1950. The slightly modified arrangement makes it easier to find the more important subjects, and the bibliography is a very useful reference work for all who are interested in research and treatment. Fairly full abstracts of the more important papers are given, with brief notices of those of less value, not only in the rheumatic and collagen diseases, but in other branches of medicine.

Copies may be obtained from the General Secretary, Empire Rheumatism Council, Tavistock House North, Tavistock Square, London, W.C.1.

The Spa in Medical Practice. Report of a Committee of the British Medical Association. 1951. B.M.A., London. 3*s.* 6*d.*

This little booklet embodies the work of a committee of the British Medical Association under the chairmanship of Lord Horder, which being composed of Consultants, Spa practitioners, General practitioners, and observers from the Ministry of Health, was well equipped to investigate the subject impartially and to furnish a report which should prove useful to practitioners, free from advertisement while giving all necessary information.

In an introductory chapter the distinctive features of spa treatment are fully discussed and stress is laid on the part it can play in convalescence and rehabilitation as well as in the management of those diseases such as gout and rheumatism for which its value is established. The reputation of the British spas dates from the mid-16th century and has steadily increased until the present day, but the reputation of spa therapy in general may reasonably be dated back to Hippocratic times when the importance of rest, fresh air in favourable climatic surroundings, and recreation for body and mind combined with physiotherapy was already recognized. The primitive methods of drinking the mineral waters and bathing therein undoubtedly established the repute of the spas which has been maintained and increased. The 18th century was marked by a remarkable output of literature on the subject, and by the establishment of the great spa hospitals which have done much to advance the treatment of chronic rheumatic diseases and later, by establishing research laboratories, to increase our knowledge of their pathology. A further stimulus was given by the work of Priessnitz in the 19th century. Though only a peasant, he gained a great reputation for his " Hydropathy ", which was established upon more scientific principles by Winternitz and Baruch, and, in Great Britain, by Fortescue Fox. The value of his methods was soon recognized in the spas; new techniques were introduced and with the dawn of the 20th century physiotherapy was added in many other forms, notably electrical treatment and remedial gymnastics.

The establishment of the National Health Service has brought spa treatment into a still wider field of usefulness. The social aspect of the annual spa cure has to a great extent given place to the hospital organization associated with attractive surroundings and amenities which promote rehabilitation in traumatic conditions and convalescence after illnesses other than those diseases for which the spas have been conspicuously noted in the past. All these features are described in the opening chapters which are full of interest. The second half of the book is devoted to descriptions of the principal spas. This supplies useful information, which might perhaps be more scientific in character, though that aspect may be considered as adequately treated in the earlier chapters on the indications for choice of spa and the various techniques employed. What is most needed now is the provision of better facilities for training doctors in the special methods of spa therapy.

C. W. BUCKLEY.

The Pituitary-Adrenocortical Function. Compiled by Karl A. Baer and Marjory Spencer, with the assistance of Paulyne Tureman and Stanley Jablonski. (1950.) Army Medical Library, Washington, D.C.

This bibliography, which reports 3,447 papers on ACTH, Cortisone, and Related Compounds, with brief abstracts from the more important articles and an index of authors, is likely to be very useful to workers in this field and to rheumatologists in particular. The action of the United States Army Medical Library in publishing this exhaustive work will be greatly appreciated.

C. W. BUCKLEY.

The Cortisone Investigator. Merck and Co. Inc., Rahway, N.J., U.S.A.

This semi-monthly publication, the first number of which appeared in June, 1950, comprises abstracts from the medical literature on cortisone and related substances. The abstracts are fairly full and informative, and the publication furnishes a very useful up-to-date guide to the literature of the subject.

C. W. BUCKLEY.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* ABSTRACTS OF WORLD SURGERY, OBSTETRICS AND GYNAECOLOGY, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Sciatica; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The new section " ACTH, Cortisone, and other Steroids ", which appears in the present issue, includes certain abstracts and titles of articles dealing with steroid research, which although not directly concerned with the rheumatic diseases, may make an important contribution to the general study of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Oral Penicillin Prophylaxis in Rheumatic Fever Patients. BRICK, M., MCKINLEY, H., GOURLEY, M., ROY, T. E., and KEITH, J. D. (1950). *Canad. med. Ass. J.*, **63**, 255. 1 fig., 7 refs.

A group of children who had suffered from rheumatic fever and who received 50,000 units of oral penicillin thrice daily for 2 years was compared with a control group of 38 similar children as regards (1) the occurrence of β-haemolytic streptococci in repeated throat cultures; (2) the number of upper respiratory infections; (3) recurrence of rheumatism. The groups were made as similar as possible as regards sex, age, and duration of illness. Blood penicillin levels in ten children after a single 50,000-unit dose averaged 11 units per ml. after one hour, 0·035 unit per ml. after 2 hours, and 0·025 unit after 3 hours.

During the 2 years of the trial, 52 throat swabs out of 576 in the control group grew β-haemolytic streptococci, but only three out of 570 in the penicillin-treated group grew the organism. The authors conclude from this that haemolytic streptococci can be largely eliminated from the throat by the above dosage, and that this would be a useful safeguard in a community of children during an epidemic. There was no epidemic during the trial. A gradual increase in the number of positive cultures occurred in the autumn and early winter, reaching a peak in March. There were 158 colds in the control series and 151 in the treated group.

There were six cases of rheumatic recurrence in the control group, including two patients with streptococci in their throat and five with a raised antistreptolysin titre. In the treated group, among the three patients with recurrence none had haemolytic streptococci in the throat but all three had a raised antistreptolysin titre. The numbers were not large enough to draw clear-cut conclusions, but there was suggestive evidence that the recurrence rate is reduced by giving penicillin. There were no cases of a rash or allergic reaction in the series.

R. Hodgkinson.

Oral Penicillin in the Prophylaxis of Recurrent Rheumatic Fever. MALINER, M. M. (1950). *J. Pediat.*, **37**, 858. 7 refs.

The author describes the use of troches containing 5,000 units of penicillin in a small group of children with rheumatism (63) or with congenital heart disease (23). Of the former 33 and of the latter thirteen were given penicillin troches to suck three times daily from September to June, the remainder acting as controls. The bacteriological results are given with such conciseness that they are difficult to comprehend. It would seem, however, that β-haemolytic streptococci were infrequently present, whereas *Staphylococcus aureus* was isolated from " 95 per cent. of all the cultures taken ". In the control group there were two recurrences and in the treated group none. The author concludes [somewhat naïvely] that " this study confirms a previous opinion that 5,000 unit penicillin throat troches are of value in temporarily eliminating *S. haemolyticus* from the throats of rheumatic children ". The condition of the staphylococci in regard to their resistance to penicillin before, during, and after the treatment does not appear to have been studied.

[This paper has no value as a contribution to the study of the prevention of recurrences of rheumatic fever.]

T. Anderson.

Relation of Hyaluronidase to Salicylates and Rheumatic Fever. JAWORSKI, A. A., FARLEY, J. E., BARRETT, J., and JAWORSKI, R. A. (1950). *J. Pediat.*, **37**, 697. 2 figs, 36 refs.

Working in Pawtucket, U.S.A., the authors have investigated the effects of salicylate and succinate on hyaluronidase activity in normal and rheumatic subjects (four showing signs of active disease and eighteen convalescent from acute rheumatism). As controls they used 22 children recovered from primary tuberculosis. The hyaluronidase was a highly purified extract of bovine testicular origin which produced no inflammation on injection. The indicator dye used was Evans blue

(T—1824). The authors made many comparisons between the spreading of the dye in rheumatic and non-rheumatic subjects with and without salicylate and succinate therapy. The area of dye spread with hyaluronidase was significantly greater in rheumatic than control subjects, thus confirming the findings of previous workers in this field. A most important finding was that in rheumatic subjects salicylate therapy had no inhibiting effect on the spreading of the dye whether hyaluronidase was injected simultaneously or not. In the non-rheumatic subjects, however, oral administration of salicylate to produce a blood level of 18·5 mg. per 100 ml. brought about a 30·4 per cent. decrease of dye spread with hyaluronidase, and a 17·8 per cent. decrease without hyaluronidase injection. Hyaluronidase is an enzyme which can be extracted not only from many tissues, but from a variety of organisms, including the streptococcus which is closely associated with rheumatic fever. The authors suggest that increased allergy to hyaluronidase may explain why some subjects develop acute rheumatism in the presence of a streptococcal infection while others do not. The significance of the observation that salicylates inhibit hyaluronidase effects in normal and not in rheumatic subjects remains undetermined. *William Hughes.*

Cardiotonic Treatment of Rheumatic Carditis in Children. (Kardiotonická léčba dětských reumatických karditid.) BUČEK, A. (1951). *Lék. Listy*, **6**, 57. 16 refs.

The Clinical Value of Blood Fibrinogen Estimations in Acute Rheumatism. (Valeur clinique du dosage du fibrinogène sanguin dans le rhumatisme articulaire aigu.) MERLEN, J. F., and DAILHEU-GEOFFROY, P. (1950). *Gaz. méd. France*, **57**, 1197. 30 refs.

The Diagnostic Value of Rose's Reaction in Primary Chronic Polyarthritis. (Valore diagnostico della reazione di Rose nella poliartrite cronica primaria.) LUCENTINI, L., and IOLI, G. (1950). *Policlinico prat.*, **57**, 1325. 5 refs.

Sodium Salicylate, a Curative and Prophylactic Agent in Rheumatic Fever. (El salicilato de sodio, medicamento profilático y curativo de la fiebre reumática.) COSTA BERTANI, G. (1950). *Rev. argent. Reum.*, **15**, 123. 22 refs.

Preliminary Report on the Treatment of Rheumatic Fever in Infancy with Sodium Gentisate. (Prime esperienze cliniche nella cura della malattia reumatica dell' infanzia con il gentisato di sodio.) TOSCANO, F. (1950). *Minerva med., Torino*, **2**, 1046. 6 refs.

Rheumatic Fever in Children. SPOHN, P. H. (1950). *Bull. Vancouver med. Ass.*, **27**, 14. 10 refs.

An Environment and Sociological Study of Rheumatic Heart Disease. In School Children from Four Connecticut Communities. QUINN, R. W., LIAO, S. J., and QUINN, J. P. (1950). *Amer. J. publ. Hlth.*, **40**, 1285. 4 figs, 8 refs.

Is Rheumatic Fever a Preventable Disease ? MCCULLOCH, H. (1951). *Illinois med. J.*, **99**, 28.

Rheumatic Fever in Hawaii. CONNOR, A., and YOSHINA, T. (1951). *Hawaii med. J.*, **10**, 181. 7 refs.

Acute Forms of Rheumatism. (Reumatismos agudos.) LÓPEZ ZAMORA, R. (1950). *Rev. argent. Reum.*, **15**, 195.

Rheumatic Heart Disease in Algerian Native Children. A Statistical Study. (Cardiopathies rhumatismales de l'enfant indigène algérien étude statistique.) SARROUY, C., and VENEZIA, R. (1950). *Pédiatrie*, **39**, 867. 9 refs.

Routes of Administration of Salicylates. (Sobre vias de administracion para la saliciloterapia.) MALDONADO, I. (1950). *Rev. argent. Reum.*, **15**, 185. 14 refs.

Studies on the Pathogenesis of Rheumatic Fever. II. A Comparison of Antibodies to Haemolytic Streptococci in Patients with Rheumatic Fever, Patients with Mild Streptococcal Infections, and Normal Control Groups. KIRSCHNER, L., and MARTIN, K. (1950). *N.Z. med. J.*, **49**, 713. 4 figs, 32 refs.

Antistreptolysin Titer as an Aid in the Diagnosis of Rheumatic Fever. BREESE, B. B., and GRAY, H. (1951). *N.Y. St. J. Med.*, **51**, 389. 16 refs.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

The Anemia of Infection. XIV. Response to Massive Doses of Intravenously Administered Saccharated Oxide of Iron. KUHNS, W. J., GUBLER, C. J., CARTWRIGHT, G. E., and WINTROBE, M. M. (1950). *J. clin. Invest.*, **29**, 1505. 11 figs, 20 refs.

Evidence of the effect of intravenous iron in the hypochromic anaemia of infection, particularly that associated with rheumatoid arthritis, is conflicting. The present authors have recently made an intensive study of fourteen cases. They conclude that despite the large doses given and a rise in serum iron level immediately following treatment, in no instance where the associated illness persisted following therapy was the hypoferremia permanently corrected. In no case was there a reticulocytosis or haemoglobin rise comparable to that found in patients with a straightforward iron deficiency. In three cases urinary iron was estimated, and in one the iron in a purulent exudate: loss of iron by these routes was not significant. In two patients who subsequently died analysis of viscera showed that an amount corresponding to 46 to 88 per cent. of the administered iron was recoverable in the liver and spleen. The reason for this diversion of iron to the tissues remains obscure. The authors suggest that since the satisfactory response obtained by Sinclair and Duthie (*Lancet*, 1949, **2**, 646; *Brit. med. J.*, 1950, **2**, 1257) was associated with a fall in erythrocyte sedimentation rate, there was possibly an equal improvement in the clinical condition of the patient, and therefore in the anaemia, which was not due to iron therapy. *Janet Vaughan.*

The Manubrio-sternal Joint in Rheumatoid Arthritis. BOGDAN, A., and CLARK, J. (1950). *Brit. med. J.*, 2, 1361. 5 figs, 5 refs.

A report is presented, from the Westminster Hospital Rheumatism Unit, of five cases of involvement of the cartilaginous manubriosternal joint in rheumatoid arthritis. Pain, swelling, and tenderness at the joint site were noted, and were aggravated by respiratory movements—particularly coughing, sneezing, and yawning. Differential diagnosis had to be made from angina in one case in which the pain was particularly aggravated by the deeper inspirations resulting from exertion. In one case the affection of this joint was the first manifestation of rheumatoid arthritis. Radiological changes are best seen in coned lateral views (of which four examples are reproduced) and occur later; they may include irregularity and narrowing of the joint space, erosion of the articular surfaces, and irregular expansion of the articulating bone ends. Progression to bony ankylosis was not observed in these cases. *Harry Coke.*

Objective Assessment of Improvement in Rheumatoid Arthritis. JANUS, O. (1950). *Brit. med. J.*, **2**, 1244. 6 figs, 12 refs.

The introduction of the potent antirheumatic agents, cortisone and adrenocorticotrophin (ACTH) has underlined the need for reliable objective tests of improvement in rheumatoid arthritis, sensitive and accurate enough to demonstrate a response to single injections of cortisone or ACTH, which would be used in estimating dosage and in comparing the effects of unknown substances, standard active preparations, and inert controls in the same patient, and which would eliminate the psychological factors involved in any subjective or clinical assessment. By measurements of joint tenderness, strength of grip, articular blood flow, finger-tip temperature, and number of circulating eosinophils in cases of rheumatoid arthritis under standard conditions, the author claims to have evolved a reliable method of objective assessment responsive to the effects of single doses of cortisone and ACTH. A new method for measuring joint tenderness in the fingers is described, and both this measurement and the measurement of grip are reproducible within a narrow range. Blood flow in involved knee-joints is measured by plethysmography, and skin temperature by thermocouples on the finger-tips. Daily measurements were carried out on patients at rest under basic conditions and those in which all readings showed steady improvement, indicating that they were going into remission on rest alone, were eliminated, only those patients whose measurements were largely unchanged over a period of several days being selected for study of the effects of treatment. After an injection of 25 mg. ACTH a lessening of joint tenderness and an increase in strength of grip, maximal between 6 and 8 hours, and a fall in the number of circulating eosinophils were demonstrated. Knee blood flow showed a biphasic response, a variable initial increase at 6 hours being followed by a rapid decrease between 8 and 12 hours after the injection. Skin temperature was unchanged. The responses to a single injection of 200 mg. cortisone were similar but slower, except that there was not the early increase in knee blood flows which was produced by ACTH. In view of this variability in response, it was decided that the measurement of knee blood flow was not suitable for inclusion in the test.

In a number of experiments, single injections of ACTH (in three different test doses), of cortisone, and of an ACTH peptide produced regular and statistically significant deviations in eosinophil count, pain threshold for joints, and strength of grip, whereas no such deviations were seen after the administration of various other drugs which have been claimed to be effective in rheumatoid arthritis, or after injections of inert substances. It was noted, however, that of ten patients tested there appeared to be some response to aspirin in three, in all of whom the drug produced eosinopenia; the eosinophil count was unchanged in the remaining seven cases. *Ellis Dresner.*

Clinical Assessment of Rapidly Acting Agents in Rheumatoid Arthritis. QUIN, C. E., MASON, R. M., and KNOWELDEN, J. (1950). *Brit. med. J.*, 2, 810. 16 refs.

This interesting investigation seems to prove that the intramuscular injection of deoxycortone acetate followed immediately by intramuscular injection of ascorbic acid has no specific, objectively demonstrable, therapeutic effect on out-patients suffering from rheumatoid arthritis. Injection of any substance, even of no therapeutic value whatever, may produce a transient subjective improvement in about two-thirds of cases of rheumatoid arthritis treated.

It has long been known that subjective improvement of this sort is to be anticipated in certain cases when a new treatment is undertaken, but that this will occur in as much as 58 per cent. of cases is of interest. Such a result emphasizes the fact that the strictest control methods are necessary to demonstrate that improvement of this sort is not in fact due to the test substance used. The authors were able to do this by proper randomization of the control injections together with certain other precautions. No significant difference could be detected after careful observation when the results of objective tests with control injections were compared with those in which the test substance was used. [Future investigators will do well to follow the criteria indicated in this well-planned investigation.] *W. S. C. Copeman.*

Insulin and E.C.T. in Treatment of Rheumatoid Arthritis. Report on a Pilot Series of Cases. KERSLEY, G. D., MANDEL, L., JEFFREY, M. R., DESMARAIS, M. H. L., and BENE, E. (1950). *Brit. med. J.*, 2, 855. 16 refs.

Insulin hypoglycaemia provokes the liberation of adrenaline, and thereby may stimulate the adrenal cortex. It is possible that this also explains the effect of electric convulsion therapy. It was decided to treat two series of cases of rheumatoid arthritis by these two methods.

Forty cases of active rheumatoid arthritis were treated five times weekly for 3 or 4 weeks by induction of hypoglycaemia with insulin. In 22 cases there was marked improvement, and in ten this was maintained for 6 weeks after completion of treatment. All the patients gained weight, but there was no significant change in the erythrocyte sedimentation rate. In 24 cases the eosinophil count fell 4½ hours after maximal hypoglycaemia, but there was no apparent correlation between the degree of hypoglycaemia, eosinopenia, and recovery. Neither was there an apparent correlation between the degree of recovery and the depression of eosinophil count provoked by adrenaline or adrenocorticotrophin.

Eleven cases were treated by electric convulsion

therapy, an average of five shocks being given. Three cases were markedly improved.

It is stressed that further control and follow-up is needed before results of these two forms of treatment can be assessed. *D. P. Nicholson.*

Serum Factor in Rheumatoid Arthritis Agglutinating Sensitised Sheep Red Cells. BALL, J. (1950). *Lancet*, **2**, 520. 6 refs.

It was reported by Rose and others (*Proc. Soc. exp. Biol., N.Y.*, 1948, **68**, 1) that serum from cases of rheumatoid arthritis agglutinated sensitized sheep erythrocytes in high dilutions, whereas normal sheep cells were agglutinated only in low dilutions. The author demonstrates that the factor responsible for agglutination in sensitized sheep erythrocytes is not the heterophil antibody, but must be an entirely different and hitherto unrecognized substance. He standardizes the duration of the test and points out that the rabbit anti-sheep-erythrocyte serum used for the sensitization of the sheep cells may not always contain equal proportions of haemolysin and of agglutinin. With a sufficiently wide margin between agglutinin and haemolysin titres, the original technique of standardizing the sensitizing serum on the basis of its haemolysin content is satisfactory, but in rare cases the agglutinin titre of the rabbit serum may be so high as to cause spontaneous agglutination of the sensitized cells. The author therefore checks the haemolysin content against a human serum of which the agglutinin titre for sensitized cells is known.

Out of 286 cases diagnosed clinically as of rheumatoid arthritis, the serum in 49 per cent. contained the factor, and in 51 per cent. it was negative. The test was negative in 97·6 per cent. of 85 cases of ankylosing spondylitis, in 98·3 per cent. of 107 cases of osteo-arthritis, and in 94·2 per cent. of 120 cases of arthritis of other types. Of 79 patients attending a rheumatism clinic suffering from indeterminate painful states such as fibrositis, all but one gave a negative reaction, while 100 per cent. negative reactions were obtained in nine cases of rheumatic fever, eight cases of acute or subacute rheumatism, and 134 cases of various non-arthritic diseases. Of 67 medical and surgical patients chosen at random, only one gave a positive reaction.

The author concludes that the factor in human serum which agglutinates sensitized sheep erythrocytes and is distinct from heterophil antibody is of considerable serological interest. It seems to be present in relatively small amounts in the sera of some apparently healthy persons as well as in various diseases, but in a proportion of cases of rheumatoid arthritis the concentration of the factor is greatly increased, with the result that the agglutination of sensitized cells may be evident when the serum is diluted a thousand times or more. He suggests that this factor may possibly be related to the disease process of rheumatoid arthritis.

From the clinical trials it is concluded that the test offers the advantage of considerable specificity, as 91·5 per cent. of the cases in which positive results were obtained had been diagnosed clinically as of rheumatoid arthritis. Further, five out of thirteen false-positive results occurred in patients with arthritic disease which might easily have been labelled " rheumatoid arthritis ". The author points out that—rheumatoid arthritis being an ill-defined clinical syndrome which merges with various arthritic, peripheral vascular, and other diseases—any test which facilitates the delineation of a single clinical group might be of value in the study of rheumatic disease. *H. Lehmann.*

Assessment of Adrenal Cortical Activity in Cases of Chronic Rheumatism after the Intravenous Administration of Large Doses of Sodium Glycerophosphate. (Esame della funzionalità cortico-surrenale in " reumatici " cronici dopo somministrazione endovenosa di glicerofosfato di sodio ad alte dosi.) NATALE, P., and PALA, A. (1950). *Policlinico (prat.)*, **57**, 1365. 20 refs.

After a brief review of the theories of the pathogenesis of chronic rheumatic disorders Selye's general adaptation syndrome in response to stress, and the alarm reaction, are discussed as being concerned with upsetting the balance of the diencephalic-pituitary-adrenocortical system, thus leading to chronic disorder of the joints. An attempt was made to determine whether the good results of large doses of sodium glycerophosphate are due to its activation of a " stress " mechanism, thereby stimulating the output of cortisone and/or adrenocorticotrophic hormone (ACTH).

Six patients with rheumatoid arthritis and two normal controls were given 10 ml. sodium glycerophosphate (2·5 g. in a 25 per cent. solution) intravenously for three consecutive days. Three days before, and for 3 days after, the injection, Thorn's test was carried out to see if there was any marked drop in the number of the eosinophils in the blood or an increase of the uric acid/creatinine ratio in the urine, indicating an excess of ACTH and/or cortisone. The results showed a complete irregularity before and after the experiment, and have to be regarded as negative. Lucherini's view that the beneficial effect of large doses of sodium glycerophosphate is perhaps due to their influence on the acid-base balance is thought to be nearer the mark.

[A study of the tabulated results of these carefully performed experiments is of much interest. The great variation in the findings even before the injections, and in the controls, should be a warning against wishful thinking and exaggerated hypotheses in connexion with indirect biochemical and biological assays of cortisone and ACTH.] *V. C. Medvei.*

Prolonged Treatment of Rheumatoid Arthritis with A.C.T.H. alone and with Gold. GOSLINGS, J., HIJMANS, W., VAN LIMPT, P. M., and VAN GILSE, H. A. (1950). *Brit. med. J.*, **2**, 1019. 5 figs, 15 refs.

In view of the established observation that the favourable effects of adrenocorticotrophin (ACTH) treatment in rheumatoid arthritis rapidly disappear when it is discontinued, and that with prolonged administration untoward side-effects tend to occur, the authors of this paper set out to find some method of combining a minimal maintenance dose of this material with one of the approved medical remedies in the hope that a remission might be induced and that no relapse would then occur after the discontinuance of the ACTH injections.

With this end in view, they treated five patients with rheumatoid arthritis and one with ankylosing spondylitis with small doses of ACTH over periods of 2 to 6 months. In four of these cases there was a completely favourable reaction, which it was found possible to maintain with six intramuscular injections of 2 mg. ACTH daily.

An attempt was then made to maintain this improved condition with injections of gold salts. Although this procedure would appear to be a reasonable one the authors were unable to decide whether it was successful in their cases, and they state that more experience with the combined treatment will be necessary before conclusions can be drawn. *W. S. C. Copeman.*

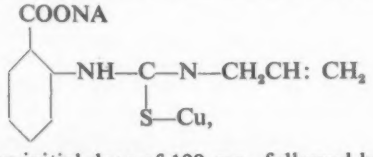
Treatment of Diseases of Dysreaction with Nitrogen Mustard. I. Rheumatoid Arthritis. (El tratamiento de las enfermedades de disreaccion con las mostazas nitrogenadas: Fundamentos y resultados. I. Tratamiento de la artritis rheumatoide.) JIMÉNEZ DÍAZ, C., MERCHANTE, A., PERIANES, J., LOPEZ GARCÍA, E., and PUIG LEAL, J. (1950). *Rev. clin. esp.*, **38**, 261. 8 figs, bibl.

The authors give a general survey of the action of adrenocorticotrophin (ACTH) in rheumatoid arthritis, and then describe in detail fourteen cases treated with nitrogen mustard. Pain and joint inflammation lessened considerably, mobility increased, and temperature returned to normal. The original dosage employed (five injections of 0·1 mg. per kg. body weight) was found to be excessive, causing anaemia, leucopenia, and in one case thrombocytopenia—all successfully treated by blood transfusion. It was later found that results as good could be obtained with a total of three doses of 4 mg. each, given on alternate days. With this dosage no haematological complications ensued.

The mechanism of action of nitrogen mustard is obscure, but is related to that of ACTH, in that the former is also antimitotic, produces lympholysis, and causes a lowering of the blood eosinophil count and an increase in the urinary excretion of 17-ketosteroids. In spite of this, the authors do not consider that nitrogen mustard acts by excitation of the adrenal cortex, but that it more likely has a direct action on mesenchymal structures and "defence organs". If Sabin's view that antibodies are formed by lymphocytes and released by lympholysis is correct, then another possible mode of action of nitrogen mustard related to its lympholytic effect must be considered. *René Méndez.*

Copper Therapy of Rheumatoid Arthritis. TYSON, T. L., HOLMES, H. H., and RAGAN, C. (1950). *Amer. J. med. Sci.*, **220**, 418. 4 refs.

This study of copper therapy in rheumatoid arthritis was undertaken because of Forestier's favourable report published in 1946. First, twenty patients with severe rheumatoid arthritis, in which gold therapy had been either ineffective or toxic, were treated by intravenous injections of "cupralene", an organic copper salt,



receiving an initial dose of 100 mg., followed by 250 mg. twice weekly until a total of 4 g. had been given. This is the dosage recommended by Forestier. No toxic effects of importance were observed. In only two cases was the condition improved.

Higher doses were used in a second course. The same patients were given 500-mg. doses once or twice a week, and seven more, with disease of less than one year's duration, after preliminary 100- and 250-mg. doses, were given the same amount, in most cases up to a total of 10 g. The results were equally disappointing, but toxic effects were very definite. The more serious of these were nausea, vomiting, and rigors coming on in from 1 to 8 hours after an injection, and severe, rapidly developing anaemia. The authors conclude that cupralene is of no value in the treatment of rheumatoid arthritis. *Kenneth Stone.*

Hematological Changes in a Case of Rheumatoid Arthritis treated with Adrenocorticotropic Hormone (ACTH, Corticotropin). [In English.] HÄVERMARK, N. G., and NORDENSON, N. G. (1950). *Acta haemat., Basel*, **4**, 193. 4 figs, 5 refs.

A 62-year-old woman with rheumatoid arthritis and anaemia (haemoglobin value 50 per cent.) was treated with adrenocorticotrophin for two periods of 31 and 20 days respectively. Serial blood counts and examinations of sternal marrow were made. During treatment, there was a slight increase in erythrocyte count and haemoglobin value with a sharp rise in serum iron level. There was also a granulocytosis, with the expected fall in eosinophil count. The bone marrow changes were not remarkable. *P. C. Reynell.*

Precipitin Reaction of Serum from Cases of Rheumatoid Arthritis with Homologous Connective Tissue Extracts. LANSBURY, J., CROSBY, W. R., and BELLO, C. T. (1950). *Amer. J. med. Sci.*, **220**, 414. 3 refs.

Complement-fixation and precipitin tests were carried out to test the hypothesis either that connective tissue in cases of rheumatoid arthritis has become antigenic and had provoked immune body formation, or that normal connective tissues are being attacked by abnormal immune bodies. Tissues—subcutaneous nodules and joint tissues—removed from six patients with rheumatoid arthritis were used as test antigens; details of preparation are given. Control antigens were prepared from tissues removed from patients without arthritis. In general, both sera from patients with rheumatoid arthritis and controls when tested with the two types of antigen gave negative complement-fixation reactions. On the other hand, a number of precipitin reactions were obtained between sera from patients with rheumatoid arthritis and antigens from such patients and from controls, control sera giving only one doubtful reaction. The negative complement-fixation reactions make it unlikely that this is a true antigen-antibody reaction; its significance is unknown. *Kenneth Stone.*

Plasma Levels of Free Amino Acids in Normal Subjects Compared with Patients with Rheumatoid Arthritis. BORDEN, A. L., WALLRAFF, E. B., BRODIE, E. C., HOLBROOK, W. P., HILL, D. F., STEPHENS, C. A. L., KENT, L. J., and KEMMERER, A. R. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 28. 11 refs.

Considerable evidence is available that abnormal metabolism of amino-acids is a frequent accompaniment of rheumatoid arthritis. The investigation reported by the authors was undertaken in order to determine whether a difference exists in the plasma content of free amino-acids as between normal individuals and patients with

rheumatoid arthritis. The levels of free arginine, glycine, histidine, lysine, phenylalanine, serine, and threonine in the plasma of groups of 21 to 40 normal subjects and of 25 to 61 patients are reported upon.

Since it is generally agreed that plasma values for these amino-acids are normally relatively constant, it would be reasonable to suppose that any significant change observed in an adequate series would be worthy of further consideration. It was found that the mean values for arginine, histidine, and threonine in the rheumatoid arthritic patients were very significantly lower than those obtained in the normal groups. The values for glycine, lysine, phenylalanine and serine were not significantly different in the two groups.

W. S. C. Copeman.

Urinary Excretion of Certain Amino Acids during ACTH and Cortisone Treatment of Rheumatoid Arthritis. BRODIE, E. C., WALLRAFF, E. B., BORDEN, A. L., HOLBROOK, W. P., STEPHENS, C. A. L., HILL, D. F., KENT, L. J., and KEMMERER, A. R. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 285. 3 refs.

The urinary excretion of free threonine, lysine, tyrosine, and arginine was estimated in 41 patients suffering with rheumatoid arthritis before and during treatment with adrenocorticotrophin (ACTH) or cortisone (on which they all subsequently improved to a varying extent), the excretion values during the control periods being compared with the average and maximum values during treatment. The authors were able to show a highly significant increase in urinary excretion of free threonine, lysine, and tyrosine in patients treated with ACTH, as calculated both from the average and maximum 24-hour excretion. Patients treated with cortisone excreted a highly significantly increased amount of threonine and tyrosine, but not of lysine, at the maximum. Arginine excretion was not increased by either drug. The cause of this increase in urinary excretion of the amino-acids under study is not known, but may possibly be associated with the metabolic changes brought about by the remission of rheumatoid arthritis.

W. S. C. Copeman.

Rheumatoid Arthritis. Partial Rehabilitation by Interval Therapy with A.C.T.H. and Cortisone. STONE, R. E., SPIES, T. D., and NIEDERMEIER, W. (1950). *Lancet*, **2**, 555. 2 figs, 9 refs.

The continued administration of adrenocorticotrophin (ACTH) may be harmful, as it may over-stimulate the adrenal glands, while that of synthetic cortisone may, on the other hand, result in some degree of adrenal atrophy (as in certain examples of Cushing's syndrome where one cortex is hyperplastic and the other hypoplastic). In view of these facts it seemed worth while to treat a series of cases of active rheumatoid arthritis with a course of ACTH, followed after an interval by a course of cortisone. During the interval, injections of prenenelone acetate, deoxycortone acetate and ascorbic acid, saline, or salicylic acid were given. Only ACTH and cortisone produced any beneficial effect.

There is no evidence that the fundamental disease process of rheumatoid arthritis is cured by this treatment, but the course of the disease is favourably influenced and all the patients treated obtained temporary remission. The authors suggest that the aim should be to treat each relapse with the minimum amount of hormone required to establish a remission, possibly using ACTH and cortisone alternately.

D. P. Nicholson.

A Study of the Lipids in Post-partum Plasma. Its Use in Rheumatoid Arthritis. GRANIRER, L. W. (1950). *Surg. Gynec. Obstet.*, **91**, 591. 3 refs.

The investigation here reported was undertaken to ascertain whether or not there was any abnormality in the lipid content of the plasma post partum which might account for the fact (Granirer, *7th internat. Congr. Rheum. Dis., New York*, 1949), that a sustained remission could be produced in rheumatoid arthritis by the administration of suitable amounts of pooled post-partum plasma. The mechanism of this effect has not yet been elucidated, but the evidence suggests that it is not due solely to steroidal factors. The subjects of the investigation were parturient patients, with no evidence of liver disease, in the obstetrical wards of the Queens General Hospital, Jamaica, Long Island. All patients were maintained on an ordinary diet and blood obtained 48 to 72 hours after delivery was pooled so that each plasma specimen represented the blood of ten mothers. Lipid estimations were determined according to the method described by Bloor.

In a group of eighty subjects the average plasma level of total lipids was 465 mg. per 100 ml., of fatty acids 355 mg. per 100 ml., and of phospholipids 8·2 mg. per 100 ml. In 250 patients the average plasma total cholesterol content was 119 mg. per 100 ml. and that of cholesterol esters 68 mg. per 100 ml. It is concluded that there is a decrease in the plasma cholesterol after delivery, which may be a reflexion of pituitary adrenocorticotrophic activity.

Lilian Raftery.

Observations on the Effect of Cortisone in Chronic Arthritis. (Beobachtungen über die Wirkung von Cortisone (17-Hydroxy-11-dehydro-corticosteron) bei chronischer Arthritis.) CERESA, F., RUBINO, G. F., and GAMMA, G. (1950). *Praxis*, **39**, 923. 4 figs.

The authors report their observations on the use of cortisone in two cases of rheumatoid arthritis and one of acute rheumatic fever. The dosage used was 200 mg. on the first day, with 100 mg. on subsequent days, given intramuscularly. In the cases of rheumatoid arthritis there was dramatic relief of pain, with return of movement and function in the affected joints, within 4 hours of the first injection. In the case of rheumatic fever, which had not responded to salicylates, there was a marked improvement on giving cortisone. In each case there was the usual return to the former state after treatment was stopped.

Cortisone produced in all three cases a slight polymorphonuclear leucocytosis, eosinopenia, slight hypertension, a rise in the blood sugar level of 20 to 30 mg. per 100 ml., and an increase in the urinary excretion of 11-oxysteroids, 17-ketosteroids, and of acid. These changes are listed in detail day by day in all three cases before, during, and after treatment. A warning of the possible ill-effects of cortisone is given.

G. S. Crockett.

Influence of Adrenocorticotrophic Hormone (ACTH) on Differences of Potential Between Synovial Fluid and Skin in Rheumatoid Arthritis. STECK, I. E., MONTGOMERY, M. M., REED, C. I., and JOSEPH, N. R. (1950). *J. appl. Physiol.*, **3**, 84. 7 refs.

In an investigation carried out at the University of Illinois, Chicago, the potential difference between the

skin and the synovial fluid of the knee-joint was determined by means of a needle electrode inserted into the cavity of the latter, and a circuit including two standard saturated potassium chloride-calomel half-cells. In five young males, aged between 20 and 30, with no evidence of rheumatoid arthritis, a difference of potential ranging from 0 to 5 mv. was recorded, the joint potential being positive in relation to the skin. In six patients with active rheumatoid arthritis, the differences ranged from 28 to 76 mv. during a control period. The joint potential in the second group fell markedly during the first hour after the administration of 25 mg. adrenocorticotrophin (ACTH), and in all cases the joint potential fell to less than 5 mv. at some time during a course in which 75 mg. ACTH was given followed by 100 mg. daily for a further 3 days. In five cases the potential difference returned to the pre-treatment level on the second or fourth day after cessation of treatment.

From these results it is concluded that " the primary effect of administration of ACTH is a metabolic process mediated through the adrenal cortex and manifesting itself as a change in bio-electric potential of the articular structures ". Since a number of types of metabolic inhibitions are known to result in the production of positive potentials, the problem here posed appears to involve the specificity of the adrenocortical hormones in affecting a given reaction known to yield positive potentials. Further experiments correlating physico-chemical and metabolic processes with potential-difference changes in experimental animals are required.

A. T. Macqueen.

The Treatment of Chronic Rheumatoid Arthritis. (Considérations sur le traitement de la polyarthrite rhumatismale chronique.) BICKEL, G. (1951). *Pr. méd.*, **59**, 59. 15 refs.

The Present Position in the Treatment of Rheumatoid Arthritis. (Où en est le traitement de la polyarthrite chronique évolutive.) MONNEROT-DUMAINE, M. (1950). *Rev. méd. Moyen Orient*, **7**, 283.

Limitations of Cortisone Acetate in Rheumatoid Arthritis. SNOWDEN, V. L. (1950). *Permanente Fdn med. Bull.*, **8**, 116. 4 refs.

Personal Experience of Cortisone in Rheumatism. The Limitations of Treatment. (Une expérience de cortisone en rhumatologie. Les limites du traitement.) DE SÈZE, S., ORDONNEAU, P., and ROBIN, J. (1950). *Rev. Rhum.*, **17**, 553.

Treatment of Rheumatoid Arthritis with Pregnenolone. STRAZZA, J. A. (1950). *J. med. Soc. N.J.*, **47**, 472. 13 refs.

Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis. MACLEAN, K. S. (1951). *Lancet*, **1**, 444. 10 refs.

The Treatment of Chronic Polyarthritis by the Parenteral Administration of Aminophenazone in High Dosage. (Erfahrungen bei der Behandlung von chronischen Polyarthritiden mit hohen Dosen parenteral zugeführten Aminophenazons.) ZINNITZ, F., and KÖLWEL, E. (1950). *Münch. med. Wschr.*, **92**, 1378. 1 fig., 5 refs.

Long-term Results of Denervation of the Carotid Sinus in Rheumatoid Arthritis. (Résultats éloignés de l'énervation sinucarotidienne dans la polyarthrite chronique progressive.) MICHOTTE, L. S. (1951). *Rev. Rhum.*, **18**, 1.

Psoriatic Arthritis. Report of a Case. PLENK, H. P. (1950). *Amer. J. Roentgenol.*, **64**, 635. 2 figs, 14 refs.

Tonsillectomy in Chronic and Postacute Rheumatoid Arthritis. [In English.] RICHTNÉR, N. G. (1950). *Acta oto-laryng., Stockh.*, **38**, 419.

Present Position of Gold Therapy in Rheumatology. (Estado actual de la auroterapia en reumatologia.) SPINDLER, S. (1950). *Rev. argent. Reum.*, **15**, 188. 13 refs.

The Use of BAL in the Treatment of Skin Reactions due to Gold Therapy. MONTGOMERY, M. M. (1950). *Ann. intern. Med.*, **33**, 915. 19 refs.

Rheumatoid Arthritis With Neutropenia, Thrombocytopenia, and Splenomegaly (Felty's Syndrome) With Improvement After Splenectomy. FERSHTAND, J. B., and HOLSAPPLE, C. K. (1950). *Tex. J. Med.*, **46**, 842. 1 fig., 16 refs.

Felty's Syndrome. Report of Two Cases Treated by Splenectomy. KANAR, E. A., HARKINS, H. N., CRONE, R. I., LYTER, C. S., and ROBINSON, A. H. (1950). *West. J. Surg. Obstet. Gynec.*, **58**, 670. 4 figs, 34 refs.

Felty's Syndrome. (La sindrome di Felty.) RENATO, A. (1950). *Med. internaz.*, **58**, 279. 26 refs.

Felty's Syndrome in Chronic Haematogenous Tuberculosis. (Felty-Syndrom bei chronischer hämatogener Tuberkulose (Splenektomie).) GABLER, E. (1951). *Wien. Z. inn. Med.*, **32**, 24. Bibl.

The Tuberculin Reaction in Different Parts of the Skin and the Sensitivity in Rheumatoid Arthritis. With Special Reference to the Technical Error in the Mantoux Reaction. [In English.] WASZ-HÖCKERT, O. (1950). *Acta paediatr. Stockh.*, Suppl. 79. 2 figs, bibl.

Surgical Treatment of Deformities of Rheumatoid Arthritis of the Forefoot and Toes. LARMON, W. A. (1951). *Quart. Bull. Nthwest. Univ. med. Sch.*, **25**, 39. 6 figs.

Electrophoretic Characterization of Serum from Rheumatoid Arthritis Patients. REID, A. F., PIKE, R. M., SULKIN, S. E., and COGGESHALL, H. C. (1951). *J. Lab. clin. Med.*, **37**, 264. 3 figs, 16 refs.

Serological Reactions in Rheumatoid Arthritis. III. Increased Agglutination of Sensitized Sheep Erythrocytes in the Presence of Normal Animal Sera. PIKE, R. M., SULKIN, S. E., and COGGESHALL, H. C. (1951). *J. Immunol.*, **66**, 107. 1 fig., 20 refs.

The Supersonic Treatment of Arthritis. (Die Ultraschallbehandlung der Arthrosen.) TSCHANNEN, F., and SONNENSCHEIN, V. (1950). *Med. Klinik*, **45**, 1500. 11 refs.

(Osteo-Arthritis)

Vertebral Osteo-arthritis and Rheumatism. (Spondylosis deformans und Rheumatismus.) COCCHI, U. (1950). *Radiol. clin., Basel*, **19**, 351. 3 figs, 24 refs.

The relationship between spinal osteo-arthritis and rheumatism has not been yet fully explained. Osteo-arthritic changes occur in the vertebrae not only in man but also in erect animals (baboon, kangaroo), and represent not inflammatory but degenerative changes. Inflammatory changes occur in the soft tissue surrounding the vertebral column, and usually follow a throat infection.

The author has studied radiography of the vertebrae of 1,017 patients. They reveal an increased incidence of osteo-arthritic changes in older patients, this increase being related to the age (in the 2nd decade, 3 per cent.; in the 5th decade, 55 per cent.; in the 8th decade, 95 per cent.).

The occupation of the patient has no material influence on the incidence and degree of osteo-arthritis. No difference was observed as regards patients with sedentary occupations and those working in the erect position. There was, however, a difference between patients employed indoors and outdoors; in the former osteo-arthritis was found in 49 per cent. of cases, and in the latter in 68 per cent. of cases. The author attributes this difference to the influence of weather conditions.

Only 78 per cent. of patients complained of symptoms related to the spine. In others osteo-arthritis was an accidental finding. Out of 81 patients radiographed because of other symptoms (tumours of the neck, goitre) and without a history suggestive of osteo-arthritis or of any specific or non-specific inflammatory process, 50 per cent. showed no changes in the spinal column, but the other 50 per cent. showed osteo-arthritic changes of various degree. There was no difference in radiological appearances between cases with symptoms and those without. The osteo-arthritic changes in the latter group, however, appeared at a later age (4 to 10 years later) than in the former group. Hence radiological evidence of osteo-arthritis is not important from the clinical point of view.

The spine is not uniformly affected, areas most exposed to strain being most commonly involved. These areas are: 4 to 7 C, 5 to 9 D, and 3 to 5 L.

Exposure to adverse weather conditions causes peri-spondylitis, which accelerates the normal "wear and tear" process in the spine. Perispondylitis improves on treatment, but osteo-arthritic changes remain unaffected by treatment or even progress.

[The author's tables of results should be studied in the original by those interested.] *W. J. Czyzewski.*

Joint Debridement for Osteoarthritis of the Knee. ISSERLIN, B. (1950). *J. Bone Jt Surg.*, **32B**, 302. 8 figs, 3 refs.

The operation of joint debridement described by the author is essentially one of synovectomy, with, in addition, the removal of osteophytes. The articular cartilage is smoothed where degenerate; the menisci are preserved if they appear healthy. A total of 35 operations are reviewed after periods of 1 to 9 years. The striking results were the relief of pain (28 knees) and the restoration of movement (full extension in 25 knees, and flexion to or beyond a right angle in 27 knees).

[This valuable procedure is one which should be more often used for the osteo-arthritic knee which resists conservative treatment.] *Norman Capener.*

Experimental and Clinical Use of Oxidized Cellulose and Cortisone in the Prevention of Excess Bone and Fibrous-tissue Formation. STINCHFIELD, F. E. (1950). *J. Bone Jt Surg.*, **32A**, 739, 766. 12 figs, 4 refs.

The author records his experience of the use of oxidized cellulose and instillation of cortisone in the prevention of excessive bone and scar tissue formation after orthopaedic procedures. Oxidized cellulose was used in 22 cases of arthroplasty of the hip, knee, elbow, or hallux. The range of movement in these cases was greater than that achieved when oxidized cellulose was not used. There was little or no new bone formation, but fibrous-tissue formation proceeded normally, or was even accelerated. Accordingly the effect of cortisone, which is known to inhibit wound healing by suppressing the growth of connective tissue, was studied in experimental arthroplasty in dogs. *Post-mortem* examination of the joints in which cortisone was used revealed a reduction in fibrous-tissue formation. The author suggests that in clinical practice fibrous-tissue formation after arthroplasty could be controlled by the use of cortisone.

(In the discussion it was suggested that although cortisone might reduce fibrous-tissue formation around joints after arthroplasty, there was a risk that it might inhibit the process of wound healing.) *J. S. Batchelor.*

Heberden's Nodes. (Heberden's knuder.) SYLVEST, O., JARLØV, N. V. (1951). *Nord. Med.*, **45**, 391. 7 refs.

(Spondylitis)

Anatomical and Radiological Study of a Case of Ankylosing Spondylitis. (Étude anatomique et radiologique d'une spondylite ankylosante.) LACHAPÈLE, A. P. (1950). *J. Radiol. Electrol.*, **31**, 665. 4 figs.

Spondylarthritis Ankylopoietica. (Spondylarthritis anchylopoietica.) JONSSON, E. (1950). *Nord. Med.*, **44**, 1705. 23 refs.

Spondylitis Ankylopoietica and Osteo-arthritis of the Vertebral Column. (Spondylose rhizomélique et spondylose déformante de la colonne vertébrale.) VAN WENT, J. M. (1950). *Rev. Rhum.*, **17**, 517.

The Early Diagnosis of Spondylarthritis Ankylopoietica. (Spondylarthritis anchylopoietica incipiens. Diagnose og behandling. II.) REITER, H. F. H., and THOMS, J. (1950). *Nord. Med.*, **44**, 1739. 2 figs, 24 refs.

The Pathological Anatomy of Spondylitis and Certain Types of Polyarthritis. (A propos de l'anatomie pathologique des spondylarthrites et de certaines polyarthrites.) HERBERT, J. J. (1950). *Rev. Rhum.*, **17**, 535. 2 figs.

Rheumatoid Spondylitis (Strümpell-Marie Arthritis). Orthopedic Management. POTTER, T. A. (1950). *Amer. Practit., Phila.*, **1**, 1129.

(Miscellaneous)

Reiter's Disease: a Case Successfully Treated with Aureomycin. KORB, H., and BROWN, E. A. (1950). *Arch. Derm. Syph., Chicago*, **62**, 391. 10 refs.

The case is reported of a man, aged 20, who first came under treatment at the Boston City Hospital in 1944 with urethritis, conjunctivitis, and arthritis of the left knee. He was treated with sulphadiazine, apparently with success. Later that year the urethral discharge, conjunctivitis, and arthritis recurred and he was again admitted to hospital. Investigation showed a leucocytosis of 12,000 per c.mm., but the condition responded to sulphadiazine as before. He was admitted for a third time in 1946 with urethritis and a swollen left knee and, shortly afterwards, the conjunctivitis again became evident. This time he was treated with penicillin and was discharged from hospital 13 days later. The condition recurred, however, after 2 months, with urethritis, conjunctivitis, and a swollen left heel. He was then treated with aureomycin, 100 mg. per kg. body weight being given in the first 24 hours, followed by 75 mg. per kg. daily for one week, after which time the daily dose was reduced to 50 mg. per kg. [total dose not stated]. Improvement was immediate and the urethral, eye, and joint symptoms cleared by the third day. When seen 25 days later he was apparently well.

It is claimed that this is the first recorded case of Reiter's disease to be treated with aureomycin. [No investigations for pleuro-pneumonia-like organisms are reported as having been undertaken either in the patient or his consort(s).]

[Reiter's disease is attracting increasing attention in the U.S.A. at a considerable interval after similar interest was aroused in Great Britain. It is noteworthy also that in the U.S.A. non-specific urethritis is regarded as much less of a problem than it is in Britain.]

R. R. Willcox.

Reiter's Syndrome: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone. OGRYZLO, M. A., and GRAHAM, W. (1950). *J. Amer. med. Ass.*, **144**, 1239. 2 figs, 12 refs.

Since Reiter's description (in 1916) of the syndrome which bears his name, its boundaries have remained ill-defined, with emphasis on the triad of urethritis, conjunctivitis, and arthritis. All but one of the cases reported hitherto have been in young adult males. The causation of the disease remains in doubt. Some workers have recovered pleuropneumonia-like organisms from the genito-urinary tract and joint fluid (though they were unable to reproduce the disease experimentally); others have suggested that the syndrome is similar to dysenteric polyarthritis with toxic manifestations.

The present authors describe the effect of pituitary adrenocorticotrophic hormone (ACTH) and cortisone on the syndrome in three cases, inert injections being given both before and after the above preparations, so that the patients were unaware of any change in treatment. The patients, whose case-histories are given, were all males, aged 29, 35, and 24 respectively. The first patient was treated with ACTH in doses of 25 mg. given intramuscularly every 6 hours for 12 days; the second with 10 mg. 4-hourly for 14 days, and the third with 25 mg. 6-hourly for 14 days. Response to ACTH was dramatic (within a few days) and relapse occurred 14 to 48 hours after discontinuing the treatment. In the third case, 8 days after withdrawal of ACTH, cortisone acetate was given intramuscularly in a dosage of 300 mg. daily for 3 days, 200 mg. for 10 days, and 150 mg. daily for 10 days, making a total of 4·4 g. The condition improved even more readily than with ACTH, amd the subsequent relapse upon withdrawal was not so severe. A few weeks later cortisone was given by mouth at 12-hourly intervals, the dosage being 300 mg. daily for 3 days, 200 mg. daily for 10 days, and 150 mg. daily for 4 days, making a total of 3·5 g.; it was as effective as when given by injection and the relapse seemed even milder. Clinical impressions were fully supported by laboratory tests. The authors point to one significant and satisfactory feature. In spite of relapse on withdrawal of treatment, the course of the disease was materially shortened in the first two cases (in which the patients recovered completely) and probably shortened in the third.

[A case which presented all the signs and symptoms of Reiter's syndrome (the only unusual feature being that the patient was a young woman) was demonstrated at the January (1951) meeting of the Heberden Society; cortisone administration was without effect, the disease actually progressing while it was being given.]

D. Preiskel.

Some Examples of the Indications for Parathyroidectomy, Particularly in Chronic Rheumatism. (Documents pour servir aux indications de la parathyroidectomie. (En particulier dans les rhumatismes chroniques.)) MALLET-GUY, P., and GUIGOU, P. (1950). *J. Méd. Lyon*, **31**, 991.

The authors of this article describe a number of cases of neurofibromatosis, sclerodermia, spinal osteomalacia, and chronic back pain due to spondylitis in which removal of the parathyroid gland on one side gave relief—in one case in which the operation was performed under local analgesia the pain vanished as the gland was removed. [They do not distinguish between osteoporosis and osteomalacia and the rationale of the operation is not discussed.] Three conditions which must be fulfilled to obtain success in cases of chronic rheumatism are that the tissue removed be shown to be parathyroid by histological examination, that there be hypercalcaemia, and that the rheumatism be confined to the spine.

G. S. Crockett.

The Shoulder-Hand Syndrome and Aortic and Coronary Disease. (Syndrome "épaule-main" et affections aortocoronariennes.) SOULIÉ, P., TRICOT, R., and DEGEORGES, M. (1950). *Sem. Hôp. Paris*, **26**, 4141. 10 figs, bibl.

After a review of the literature on the shoulder-hand syndrome, four cases observed by the authors are described. Three of the patients developed the typical signs and symptoms of the syndrome after an attack of myocardial infarction, and the fourth had syphilitic aortitis with severe retrosternal pain and dyspnoea. This last patient died and necropsy revealed, in addition to the cardiac and aortic changes, microscopic lesions of a proliferative type in the region of the last two cervical and first dorsal nerve roots, with some degenerative changes in the corresponding spinal ganglia.

After describing the general course, progress, radiological appearances, and treatment of the condition, the authors discuss its aetiology in some detail. It is considered that the most probable cause is reflex sympathetic inhibition affecting the upper dorsal and stellate ganglia and that this is confirmed to some extent by the post-mortem findings. *Kathleen M. Lawther.*

Accessory Sacroiliac Articulations with Arthritic Changes. HADLEY, L. A. (1950). *Radiology*, **55**, 403. 9 figs, 3 refs.

Accessory articulations may frequently be demonstrated between the ilium and the posterior surface of the sacrum. These joints may show arthritic changes of lesser or greater degree, and ankylosis may occur. Many of the patients complain of low backache, and some of tenderness when pressure is applied over the accessory joint. Photographs of two osteological specimens and radiographs of six patients with accessory sacro-iliac articulations are reproduced, illustrating asymptomatic, arthritic, and ankylosed joints.

A. Orley.

Comparison of Muscle Biopsies and Bone Marrow Examinations in Dermatomyositis and Lupus Erythematosus. MADDEN, J. F. (1950). *Arch. Derm. Syph., Chicago*, **62**, 192. 7 figs, 20 refs.

This work was undertaken in an attempt to facilitate the differentiation between dermatomyositis and acute disseminated lupus erythematosus, which is sometimes difficult in the early stages of these diseases. Muscle biopsies were performed in eight cases of dermatomyositis, eleven cases of acute disseminated lupus erythematosus, six cases of subacute lupus erythematosus, and one case of chronic discoid lupus erythematosus.

Some degree of nodular myositis was found in all cases of dermatomyositis, but this change was also found in those cases of disseminated lupus erythematosus in which joint or muscle pains occurred. It is concluded that although muscle biopsy may help in the diagnosis of dermatomyositis it does not provide a means of differentiation when this is difficult clinically. On the other hand, the finding of the L.E. cell in bone-marrow preparations is diagnostic of acute disseminated lupus erythematosus, although it is not present in every case and is more easily found in the acute and early stages of the disease than later on. It was not found in any case of dermatomyositis or of subacute or chronic discoid lupus erythematosus. *H. R. Vickers.*

Review of Cases of Arthritis since July, 1946. (Revue des cas d'arthrite depuis juillet 1946.) ROUSSEAU, J., and DELISLE, C. (1950). *Laval méd.*, **15**, 913. 8 refs.

Chronic Rheumatic Arthritis and Housing Conditions. [In English.] DAHLBERG, G., and GRUBB, I. (1951). *Acta genet., Basel*, **2**, 42. 6 refs.

Medical Aspects of Bone Disease with Particular Reference to Osteoporosis. HOWARD, R. P. (1950). *Canad. med. Ass. J.*, **63**, 258. 8 figs, 13 refs.

The Treatment of Rheumatism with Penicillin. (Penicillinbehandlung des Rheumatismus.) EPPING, H. (1950). *Ther. d. Gegenw.*, **89**, 373.

Results to be Expected from Crenotherapy in Rheumatic Disease. (Ce que l'on peut attendre de la crenothérapie des affections rhumatismales.) JUSTIN-BESANÇON, J., and RUBENS-DUVAL, A. (1950). *Concours méd.*, **72**, 3317.

Changes in Blood Histamine Level in Arthritis after Mud-pack Treatment. (Sul comportamento dell'istaminemia negli artropatici dopo un fango.) BONESSA, C., and BOCCONI, G. (1950). *Minerva med., Torino*, **41**, 1209. 3 figs, 10 refs.

Changes in Blood Histamine Level during Mud-pack Treatment. (Sul comportamento dell'istaminemia durante la cura di fanghi.) BOCCONI, G., and BONESSA, C. (1950). *Minerva med., Torino*, **41**, 1214. 6 figs.

Physostigmine. The Clinical Response in Arthritis of Long Standing. SHAPIRO, S., and WEINER, M. (1950). *Med. Times., N.Y.*, **78**, 557. 6 refs.

The Use of Physostigmine and Foreign Protein Therapy in Arthritis and Related Conditions. STAHMER, A. H. (1950). *Wis. med. J.*, **49**, 1020. 2 figs, 10 refs.

The Therapeutic Effect of " Benzedrine " in Obesity with Rheumatism. (Les effets thérapeutiques de la benzédrine (amphétamine) chez les obèses rhumatisants.) JUNET, R. (1950). *Rev. méd. Suisse rom.*, **70**, 713.

The Problem of Effective Salicylate Therapy. (Zur Frage einer wirksamen Salizyltherapie.) MLCZOCH, F., and TREMI, E. (1950). *Wien. klin. Wschr.*, **62**, 975. 2 figs, 9 refs.

Calciferol Intoxication during the Treatment of Chronic Arthritis. (Intoxikace calciferolem při léčbě chronické arthritidy.) KUBIČKA, J. (1951). *Čas. Lék. čes.*, 90, 137. 12 refs.

Reiter's Syndrome in Childhood. CORNER, B. D. (1950). *Arch. Dis. Childh.*, **25**, 398. 2 figs, 24 refs.

Gonococcal Rheumatism as a Clinical Entity. (Le rhumatisme blennorrhagique n'est pas un vain mot.) WEIL, M. P. (1950). *Rev. Rhum.*, **17**, 562.

Ten Cases of Amoebiasis with Arthritic Complaints. ZINNEMAN, H. H. (1950). *Amer. J. Digest. Dis.*, **17**, 342. 16 refs.

The Significance of Acute Lumbago. (Le lumbago aigu. Sa signification.) LIÈVRE, J. A. (1950). *Rev. Rhum.*, **17**, 557. 12 refs.

The Aetiology of Certain Types of Arthritis of the Hip. (L'étiologie de certaines arthroses de la hanche.) CHARRY, R. (1950). *Rhumatologie*, No. **5**, 220. 7 figs.

Periarthritis of the Shoulder. (La périarthrite de l'épaule.) SICHÈRE, R. M. (1950). *Méd. franç., Paris*, **10**, 263.

Scapulo-humeral Periarthritis of Coronary Origin. (Les périarthrites scapulo-humérales d'origine coronarienne.) RUELLE, M. (1950). *Rev. Rhum.*, **17**, 515.

Anatomical Aspects of Scapulo-humeral Periarthritis. (Les aspects anatomiques de la périarthrite scapulo-humérale.) DENIS, A. (1951). *Rev. Rhum.*, **18**, 22.

Scapulohumeral Periarthritis. (Periarthritis scapulohumeralis.) BUYSE, K. (1951). *Belg. Tijdschr. Geneesk.*, 7, 193. 2 figs.

Sciatica

Anomalies of the Lumbosacral Vertebrae in Five Hundred and Fifty Individuals without Symptoms Referable to the Low Back. SOUTHWORTH, J. D., and BERSACK, S. R. (1950). *Amer. J. Roentgenol.*, **64**, 624. 3 figs, 13 refs.

The authors review the radiological findings in the lumbar spine of 550 patients referred for barium-meal examination at the Mt. Alto Veterans' Hospital, Washington, D.C., in order to assess the clinical significance of the common variations found in this region.

The length and width of the transverse processes of the lower lumbar vertebrae were measured. The maximum width for those of L4 and L5 were found to be 14 and 19 mm. respectively, values exceeding 19 mm. for L5 being considered to indicate an attempt at sacralization. L4 could be identified by the fact that its transverse processes were smaller and more sharply angulated upward than those of L3. Asymmetry of the planes of the posterior articular facets between L4 and L5 and L5 and S1 was found in 36·4 per cent. of subjects. As none of these complained of symptoms it is concluded that such asymmetry, though mechanically undesirable, is not necessarily significant.

Some degree of spina bifida occulta occurred in 18·2 per cent. of subjects, but the incidence of scoliosis was no higher in these cases than in the rest of the series. In 6·4 per cent. of subjects there was evidence of sacralization of L5 in the form of grossly overdeveloped and wing-shaped transverse processes. Lumbarization of S1 was found in 2 per cent., and first lumbar ribs in 11·3 per cent. The incidence of osteo-arthritis appeared to be mainly related to age, but was slightly more frequent in patients with scoliosis. It was found rather often between the contiguous margins of the sacrum and sacralized transverse processes of L5. Otherwise the condition did not appear to be associated with congenital anomalies. *J. A. Shiers.*

Protrusions of Intervertebral Discs. Study of their Distribution, Characteristics and Effects on the Nervous System. HALEY, J. C., and PERRY, J. H. (1950). *Amer. J. Surg.*, **80**, 394. 9 figs, 29 refs.

The authors examined the spinal column in 99 cadavers and found protrusion of intervertebral disks in 63. Cervical protrusion was seen twice as often as lumbar, which, in turn, was seen four times as often as thoracic protrusion. The commonest sites were the 4th, 5th, and 6th cervical disks and the 4th and 5th lumbar disks. In nearly half the specimens there were multiple lesions. Many protrusions showed no rupture of the annulus, which was merely bulged. It is suggested that certain cord changes may result from compression or occlusion of spinal branches of the vertebral artery or aorta as a result of disk protrusion, and that there is no simple rule whereby the degree of neural damage may be assessed from the size, site, or nature of a disk lesion.

[The cadavers studied were dissecting-room subjects whose ages are not stated, nor are the methods and time of preservation mentioned; measurements, which are recorded in millimetres, would thus appear to be liable to wide limits of error.] *Lambert Rogers.*

Sciatica. OLIVER, L. C. (1951). *Postgrad. med. J.*, **27**, 50. 3 figs, 2 refs.

Gout

ACTH and Colchicine in the Clinical Treatment of Acute Gouty Arthritis. Physiological Considerations and Review of Therapeutic Results in Fifty-one Attacks. WOLFSON, B. Q., HUNT, H. D., COHN, C., ROBINSON, W. D., and DUFF, I. F. (1950). *J. Mich. med. Soc.*, **49**, 1058 and 1083. 1 fig., 18 refs.

Adrenocorticotrophin (ACTH), given in doses small enough to be free from undesirable effects, will end almost all acute attacks of gout within 24 hours. When the hormone is withdrawn some patients relapse within a few days, but this is found to be prevented by the simultaneous administration of colchicine. In this study three preparations of ACTH were used: (1) aqueous ACTH; (2) a long-acting preparation of ACTH adsorbed on colloidal aluminium phosphate; (3) a new long-acting preparation named " polyvinyl-adactar " (ACTH adsorbed on aluminium phosphate in polyvinyl-pyrrolidone).

Patients treated with the first two preparations received an initial dose of 50 mg. which was repeated at 6-hour intervals until 75 to 90 per cent. improvement was observed. Administration of colchicine was started at the same time in a dose of $\frac{1}{100}$ grain (0·65 mg.) four times daily, which was continued until diarrhoea occurred, when it was stopped; with recovery from the diarrhoea it was resumed at a lower dosage, the process being repeated until the maximum daily dose which was well tolerated was ascertained, and this was continued for at least 2 weeks after all residual joint soreness had disappeared. The results of eosinophil counts in the peripheral blood, taken before, and 4 hours after, each dose of ACTH, and determinations of the urine urate/creatinine ratio, in 1-hour urine samples taken before, and during the 4th hour after, each dose suggest that a good therapeutic response is not obtained until ACTH evokes a good increase in adrenal function. Clinically, little change is noted for 2 to 3 hours after the initial 50-mg. dose of ACTH. Then, in patients who respond well, subsidence is rapid. In other cases there may be no change until the second or third dose is given, when there may be either the same rapid improvement or a more gradual recession. The emotional state which commonly precedes and accompanies acute gout is dissipated as rapidly as the joint symptoms. In a series of 38 attacks treated by the authors 75 to 90 per cent. improvement was generally obtained within 24 hours.

Patients treated with polyvinyl-adactar were given an initial dose of 100 mg., which was repeated at 24-hour intervals until 75 to 90 per cent. improvement was noted. This preparation appears to be active up to 48 hours after a single dose. Colchicine was given simultaneously in the manner already described. Of thirteen attacks

treated (five not previously treated with colchicine, eight colchicine-resistant attacks), all but one were terminated by a single injection of the ACTH preparation, and in eleven of the attacks 75 per cent. improvement was apparent after 12 hours. *Kenneth Stone.*

Renal Changes in Gout. BROWN, J., and MALLORY, G. K. (1950). *New Engl. J. Med.*, **243**, 325. 5 figs, 17 refs.

This survey is based on a study of five patients with gout and one patient aged 83 without clinical gout in whose kidneys urate deposits were found at necropsy. The authors believe that urates are first precipitated in the tubules, and that subsequent necrosis and fibrosis of the tubular wall may confuse the picture; this would account for previous reports of interstitial deposits. In three of their six cases there was pyelonephritis, and the lesions were most definite in relation to urate deposits blocking the tubules. It is suggested that associated pyelonephritis, as well as vascular degeneration, may play a part in the genesis of renal failure in gouty persons. *D. A. K. Black.*

ACTH and Colchicine in Therapy of Gout. Report of a Case of Acute Gouty Arthritis. LEOPOLD, H. N. (1950). *Texas J. Med.*, **46**, 710. 10 refs.

Gout in Argentine Hospitals. (La gota en nuestro medio hospitalario.) FRANCE, O., and LOSADA, M. (1950). *Rev. argent. Reum.*, **15**, 116. 14 refs.

Excretion of 17-ketosteroids in Gout. (Eliminacion de 17 cetosteroides en gota.) TARNOPOLSKY, S., MONTUORI, E., and SCHERE, M. (1950). *Rev. Asoc. méd. argent.*, **64**, 541. 5 refs.

Non-Articular Rheumatism

Chronic Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease). Relation to Rheumatic Fever and Allied Disease. BRUDNO, J. C. (1950). *New Engl. J. Med.*, **243**, 513. 5 figs, 24 refs.

A case of Weber-Christian disease is recorded. This is an uncommon syndrome characterized by successive crops of nodules in the subcutaneous (and sometimes internal) fatty tissue, associated with fever. As long as there are nodules present, fever persists. The nodules, single or in clusters and mainly on the thighs, are caused by a focal inflammatory process. Histologically, the early changes are oedema, congestion, infiltration with segmented cells and lymphocytes, necrosis of fat, and phagocytosis of fat droplets by large histiocytes; later there is replacement by collagen, and ultimately fibrosis. The overlying skin is at first red and raised; with involution of the nodule it becomes pigmented and depressed.

The case reported occurred in a woman aged 29, who was admitted to the City Hospital, Quincy, Massachusetts, with migratory joint pain and fever, and gave a past history of rheumatic fever. The author suggests that Weber-Christian disease is not a disease entity, but an allergic reaction with focal manifestations in the subcutaneous or intra-peritoneal fat, and that it is allied to the group of collagen diseases. *Kenneth Stone.*

Chronic Polymyositis. [In English.] CHRISTENSEN, E., and LEVISON, H. (1950). *Acta psychiat., Kbh.*, 25, 137. 28 refs.

Dermatomyositis is a well-recognized condition, but reports in the literature on pure myositis are infrequent. The author describes six cases of the latter.

Family histories were negative in all cases, two of which were in males and four in females. Symptoms had been present for 6 months to 10 years—in a boy of 9 since birth. The main complaints were of pain, weakness, and tenderness of muscles, with predominant involvement of the limbs and back. Rarely the facial, oculomotor, and pharyngeal muscles were affected. Atrophy of muscles was common but pseudohypertrophy was seen in two cases.

Muscle biopsy examination was performed in all cases, with the finding of fibrillary atrophy, lymphocytic infiltration (frequently perivascular), and a less marked cellular exudate of mononuclears, polymorphonuclear, or eosinophil cells. In two cases biopsy was repeated after a course of streptomycin and the cellular infiltration was then found to be much reduced. In four of the cases streptomycin led to improvement and to a fall in the erythrocyte sedimentation rate.

Proximal muscles were mainly affected, as in a dystrophy, and in three cases a clinical distinction from muscle dystrophy was impossible; the electromyographic findings were also compatible with a dystrophy. In two cases the initial biopsy diagnosis was myositis, but re-examination of a specimen after an interval showed the picture of a dystrophy.

In myositis, streptomycin may lead to improvement or complete remission. Some cases of muscular dystrophy may be the late result of an attack of myositis.

[From the clinical and microscopical descriptions given, the abstracter finds it difficult to withhold the diagnosis of muscular dystrophy in some of these cases.] *D. P. Jones.*

Panniculitis. Report of Cases. JONES, P. E., LAMB, J. H., and GOLDMAN, L. (1950). *Sth. med. Jl, Bgham., Ala.*, **43**, 792. 7 figs, 14 refs.

An outline of the features of panniculitis, and of the 34 cases described in the literature, is given, three personal cases being reported. The first patient was a woman with a history of tender tumours on arms and legs for 9 years. After *x*-ray treatment for menorrhagia she became ill and the fatty tumours broke down and discharged pus. New lesions appeared and became necrotic: she became progressively weaker and eventually died. The other two cases were both of fat necrosis of the new-born. The first child had a fatty tumour of the back which had almost disappeared at 3 months. The other had firm nodular bluish masses on the shoulders, which from time to time turned yellowish and became less firm. They gradually disappeared. All cases were associated with pyrexia. In all cases, microscopy showed necrosis of tissue fat and foreign-body cell reaction. It is noted that one child was born to a diabetic mother, while the other mother died of fat embolism a few days after delivery. The hypothesis that changed fat metabolism causes foreign-body reaction is discussed. *E. H. Johnson.*

Objective Diagnosis and Curability of Non-Articular Rheumatism. GOOD, M. G. (1951). *Brit. J. phys. Med.*, **14**, 1. 9 figs, 20 refs.

The Painful Back. BAGNALL, A. W. (1951). *Canad. med. Ass. J.*, **64**, 107.

Neurotrophic Rheumatism of the Upper Limb. (Le rhumatisme neurotrophique du membre superieur.) RAVAULT, P. P. (1951). *Rev. Rhum.*, **18**, 74. 32 refs.

General Pathology

The Uroprecipitation Reaction in Rheumatic Disease. (Odczyn uroprecypitacyjny w chorobie gośćcowej.) HIRSZFELDOWA, H., and SZOMSKA, J. (1950). *Polsk. Tyg. lek.*, **5**, 932. 4 refs.

The uroprecipitation reaction was studied in 123 cases of rheumatism. Positive results were obtained in 54 cases. Both auto- and iso-uroprecipitation have been observed by other workers in a variety of diseases (pneumonia, jaundice, typhoid fever, typhus) but in low titre (1 in 2, 1 in 4, occasionally 1 in 8), whereas in cases of rheumatic disease the titre was usually 1 in 32 to 1 in 64.

The authors recommend for the test 0·2 ml. inactivated serum from the patient, superimposed on 0·5 ml. boiled and filtered urine. After this combination has been incubated at 37° C. for 18 hours, the results are read in an agglutinoscope. Controls include saline and serum, and saline and urine. *J. W. Czekalowski.*

A Comparative Study of Antihyaluronidase, Antistreptolysin "O", Antistreptokinase, and Streptococcal Agglutination Titres in Patients with Rheumatic Fever, Acute Hemolytic Streptococcal Infections, Rheumatoid Arthritis and Non-rheumatoid Forms of Arthritis. QUINN, R. W., and LIAO, S. J. (1950). *J. clin. Invest.*, **29**, 1156. 12 figs, 45 refs.

The authors made a comparative study of the antibodies liberated in the body as a result of haemolytic streptococcal infection. Quantitative tests for the presence of these antibodies in the blood were made in the following groups: (1) patients with, and convalescent from, acute β-haemolytic streptococcal infections; (2) patients with active rheumatic fever; (3) patients with inactive rheumatic fever; (4) patients with rheumatoid arthritis; (5) patients with non-rheumatoid forms of arthritis; (6) normal subjects. The anti-bodies studied were: (*a*) antistreptolysin "O"; (*b*) antistreptokinase; (*c*) antihyaluronidase; (*d*) agglutinins to autoclaved streptococci.

A rise in titre was observed for all the antibodies in patients suffering and convalescent from haemolytic streptococcal infection and active rheumatic fever. Those with rheumatoid arthritis only showed a significant rise in the agglutinin titre, and those with non-rheumatoid forms of arthritis showed no consistent change in antibody titre as compared with normal subjects. It is suggested that these differences in antibody pattern are indicative of fundamental differences between the diseases, and might be used as the basis of a test for the diagnosis of acute rheumatism, provided recent infection with haemolytic streptococci is excluded. *S. Karani.*

Sickle Cell Anemia Simulating Rheumatic Fever in the White Race. CACCAMO, L. P., and STRUTNER, L. A. (1951). *Ohio St. med. J.*, **47**, 121. 4 figs, 11 refs.

The Pathological Anatomy Underlying Rheumatic Diseases. (Das pathologisch-anatomische Substrat rheumatischer Erkrankungen.) WALTHARD, B. (1951). *Z. Rheumaforsch.*, **10**, 39. 8 figs, 1 ref.

ACTH, Cortisone, and Other Steroids

Use of Cortisone and Adrenocorticotropic Hormone in Acute Disseminated Lupus Erythematosus. SOFFER, L. J., LEVITT, M. F., and BAEHR, G. (1950). *Arch. intern. Med.*, **86**, 558. 5 figs, 8 refs.

A series of fourteen patients with disseminated lupus erythematosus were treated with cortisone and adrenocorticotrophin (ACTH). On the whole, ACTH was quicker in its action but its effect terminated very abruptly when it was withheld. All fourteen showed dramatic improvement in the characteristic clinical features of the disease, namely, fever, weakness, joint pains, characteristic eruption, and cardiovascular changes. There was, however, little change in the biochemical findings in the patients under treatment, the effect apparently being a matter of simple clinical improvement without arrest of the essential disease processes. All fourteen patients had some oedema, hypertension, heart failure, and either depression or euphoria. Of the fourteen patients, one died in convulsions under treatment, one died from an intercurrent unrelated malady, and in one diabetes mellitus developed. Treatment was continued for several months but all the patients who survived promptly relapsed when the treatment was stopped. It is quite clear that considerable further study of this clinical enterprise is needed. *G. F. Walker.*

The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on the Course of Disseminated Lupus Erythematosus and Periarteritis Nodosa. CAREY, R. A., HARVEY, A. M., and HOWARD, J. E. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 425. 11 figs, 14 refs.

The authors describe their experience with adrenocorticotrophic hormone (ACTH) in eight patients suffering from disseminated lupus erythematosus. The initial daily dose was 100 mg., reduced gradually to 20 or 10 mg., and the period of treatment was 15 to 68 days. To four other patients suffering from the same condition the authors gave cortisone in initial doses of 200 to 400 mg., reduced gradually and continued for 11 to 18 days. The patients had had the disease for periods varying from 1 month to 8 years, with an average of 2 years. In all cases there were systemic features as well as skin lesions. All the patients responded immediately and dramatically to administration of ACTH or cortisone, the temperature becoming normal and the joint pains disappearing within 24 hours. An increased sense of well-being, loss of fatigue, and increase in appetite were noted, together with recession of skin lesions, absorption of pleural and pericardial effusions, and subsidence of palpable lymph nodes. Temporary relapse occurred in five cases, with recrudescence of fever and of skin and joint lesions, when the dose of ACTH was reduced to less than 40 mg. daily. This "rebound

phenomenon" subsided spontaneously in 7 to 15 days. Up to the time of the present report five patients had had remissions lasting from 3 to 11 months. In five there was a relapse of varying severity from 7 days to 4 months after treatment; two of these patients had a further course of treatment, which was followed by a relapse after 7 days in 1 case and a remission lasting 6 months in the other. There were two deaths, one from empyema, the other from renal insufficiency.

In five other patients (four of whom received ACTH and one cortisone) with predominant skin manifestations and no significant systemic involvement the response was less satisfactory. There was some 40 to 50 per cent. improvement in chronic lesions, but relapse occurred soon after treatment was discontinued.

Neutrophilia and lymphopenia followed administration of ACTH or cortisone, but eosinophils were already greatly reduced in number or absent before treatment was begun in most cases and therefore did not form a satisfactory index of response. The erythrocyte sedimentation rate fell to normal in seven cases and was unchanged in 10, there being a quantitative relation with the degree of clinical response and the duration of remission. Hargreaves's "L.E." cells were reduced in the peripheral blood during treatment, and serum gamma-globulin concentration fell strikingly.

One case of periarteritis nodosa is also reported in which recurrent episodes of the disease each responded in turn to three separate courses of ACTH, as shown both clinically and by serial muscle biopsy.

Robert de Mowbray.

Hypoadrenalism: Steroidal Mediation of Sodium Action on Blood Pressure; Modification of Antiarthritic Response to Cortisone. PERERA, G. A., and RAGAN, C. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 99. 1 fig., 15 refs.

This paper by workers from the Presbyterian Hospital, New York, describes studies undertaken on a patient who had had hypertension, mild diabetes mellitus, and rheumatoid arthritis, and who had more recently developed Addison's disease. Throughout the studies sufficient salt was given to maintain normal sodium values in the serum.

A dose of 25 mg. cortisone daily was sufficient to improve the arthritis without causing hypertension. With a constant sodium chloride intake, increase of the dose of cortisone or addition of deoxycortone acetate (DCA) caused haemodilution and hypertension, which subsided on withdrawal of the hormones. During the intervals between hormone therapy a rise in sodium chloride intake was accompanied by haemodilution but not by hypertension. When, however, the patient was given 1 mg. DCA daily, increase in the salt intake was accompanied by both haemodilution and hypertension. It is suggested that the action of sodium chloride on blood pressure is mediated by the adrenals. *G. Ansell.*

Effect of ACTH on Induced Fever. KASS, E. H., and FINLAND, M. (1950). *New Engl. J. Med.*, **243**, 693. 3 figs, 6 refs.

The duration and intensity of fever induced by intravenous injection of killed typhoid bacilli were studied in two cases of chronic rheumatoid arthritis at the City Hospital, Boston. Pretreatment with a few doses of adrenocorticotrophin (ACTH, 12·5 to 50·0 mg.) resulted in a diminished response as measured in "fever units", one fever unit being defined as a rise of 1° F. (0·56° C.) over 100° F. (37·8° C.) maintained for one hour. A similar effect was observed in rabbits in the response to injections of typhoid bacilli or influenza virus.

The authors conclude from their experiments that in some patients the administration of ACTH will result in reduction in fever, but no alteration in the fundamental pathological process of the illness which is being treated. [The original article should be consulted for the clinical details.] *N. R. W. Taylor.*

Development of Hypercholesteremia during Cortisone and ACTH Therapy. ADLERSBERG, D., SCHAEFFER, L., and DRACHMAN, S. R. (1950). *J. Amer. med. Ass.*, **144**, 909. 3 figs, 5 refs.

An investigation is reported of the serum cholesterol level in a number of patients undergoing treatment with cortisone or adrenocorticotrophin (ACTH) for a wide variety of diseases. Total and esterified cholesterol was determined by the method of Sperry and Schoenheimer.

Of 26 courses of cortisone acetate administered to 22 subjects, 21 were accompanied by high cholesterol levels, both total and esterified. Elevation of serum cholesterol also occurred in fifteen out of 21 courses of ACTH therapy. Of eight patients who received hormone treatment for longer than 60 days, seven developed hypercholesterolaemia (over 280 mg. per 100 ml.); the incidence was much lower in those patients on shorter courses. If hormone therapy was reduced or terminated the serum cholesterol level often fell with the recurrence of symptoms, and on resuming treatment the amelioration of symptoms was usually accompanied by elevation of the cholesterol level. Consistent parallelism between the serum phospholipid and cholesterol levels was observed. Cortisone appeared to be more effective than ACTH in producing sustained hypercholesterolaemia. Investigation of the families of some of the patients concerned showed that hereditary hypercholesterolaemia was present in only two of the eight subjects undergoing prolonged hormone treatment.

It has now been demonstrated that prolonged administration of adrenal cortical agents (cortisone and ACTH) can produce sustained hypercholesterolaemia, as can suppression of normal thyroid function. Abnormal distribution of body fat and elevation of serum cholesterol level, characteristics of Cushing's syndrome, are frequently observed in patients undergoing long courses of treatment. Moreover, premature atherosclerosis (associated with hypercholesterolaemia), often observed in Cushing's syndrome, may be induced by such treatment. Animal experiments to test this possibility are in progress. *Nancy Gough.*

Hormone Studies in Peptic Ulcer. Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone. SANDWEISS, D. J., SALTZSTEIN, H. C., SCHEINBERG, S. R., and PARKS, A. (1950). *J. Amer. med. Ass.*, **144**, 1436. 26 refs.

The authors present a preliminary report on the effect of adrenocorticotrophic hormone (ACTH) and cortisone

in the treatment of peptic ulcer. The effect of this hormone was tested on twelve dogs in whom experimental ulcers had been produced by the Mann-Williamson operative technique and on eleven control animals: 10 mg. cortisone acetate was given subcutaneously or intramuscularly twice daily throughout the life of the animal and this treatment started 13 to 30 days after operation. The dosage of ACTH used was 5 to 7·5 mg. by either route twice daily and was commenced 8 to 35 days after operation.

It was found that the dogs treated with cortisone lived, on an average, twice as long as the control animals. Those treated with ACTH lived longer than the controls, but not so long as the cortisone-treated animals. The treated animals as a group were in a good state of nutrition and vigour as compared with the untreated ones. Similar results were obtained in Mann-Williamson dogs treated with an extract made from pregnant mare's urine (" wroanthelone ", " kutrol ") which indicates that this effect of cortisone and ACTH is not specific.

The urinary excretion of 11-oxycorticosteroids and 17-ketosteroids was studied in 31 normal subjects and fourteen patients suffering from duodenal ulcer. In twelve of the latter steroid excretion was studied during an attack and repeated during a remission of symptoms. Those with active duodenal ulcer showed a statistically significant diminution of urinary excretion of 11-oxycorticosteroids as compared with normal subjects, and as compared with their excretion during a symptom-free period. This finding indicates that there is diminished adrenal activity during the active phase in duodenal ulcer.

Treatment of active duodenal ulcer with these hormones was carried out on four patients, two of whom received 1,300 mg. cortisone over a period of 11 days. One failed to respond, but the other became symptom-free with marked feelings of well-being, which continued up to 9 months after treatment. In both cases there was a decided response to the cortisone as shown by increased steroid excretion and fall in the eosinophil count.

In treating two patients with ACTH the first received 100 mg. per day (33·3 mg. 8-hourly by intramuscular injection). On the 4th day of treatment the symptoms became worse and by the 9th day had reached the stage of impending perforation; hormone treatment was then stopped. The second patient was given a dosage of 15 mg. 6-hourly for 4 days, 20 mg. 4-hourly for 4 days, 25 mg. 4-hourly for 2 days, and finally 33·3 mg. 8-hourly for 6 days. Symptoms abated on the 5th day and after the 12th day the patient became symptom-free. A few days after discharge from hospital the symptoms recurred. The response to the administration of ACTH was marked by an increased urinary excretion of steroids and a lowering of the eosinophil count.

From the material available the authors are of the opinion that, in peptic ulcer, cortisone by injection or pregnant mare's urine given orally might be of value before resorting to surgical measures, but that pituitary adrenocorticotrophic hormone should be used guardedly, if at all. *M. Beaton.*

Effects of Pituitary Adrenocorticotropic Hormone (ACTH) on the Hypersensitive State. HOWARD, J. E., HARVEY, A. M., CAREY, R. A., and WINKENWERDER, W. L. (1950). *J. Amer. med. Ass.*, **144**, 1347. 7 refs.

The effects of adrenocorticotrophin (ACTH) and cortisone in 23 cases of asthma, five of serum sickness due to penicillin, two of sympathetic ophthalmia, and two of atropine sensitivity are described. The ACTH was usually given in doses of 100 mg. daily, diminishing gradually after 2 days to 20 mg., in four divided doses. The course lasted 6 to 21 days, the total dose ranging from 193 to 1,248 mg.

Only four of the nineteen chronic asthmatics so treated were not completely relieved, and two of these were given, in error, only half the above dose. Relief lasted from 3 to 263 days, the smaller doses on the whole giving least relief. When the asthma recurred it is claimed that it was less severe than before treatment, and six patients received a second course with as much relief as after the first. The eosinophil count tended to fall from the 2nd to 7th days, but rose later when the dose of ACTH was below 30 mg. daily. Skin-test reactions were reduced in severity and nasal mucosae appeared improved. Five patients with asthma who were given cortisone, 200 mg. daily for one day and then 100 mg. for 7 days, did not do well, only one with mild disease being relieved. Subsequently three of these patients responded to ACTH.

Four patients with penicillin reactions improved within 12 hours and the symptoms had disappeared after 72 hours with ACTH in doses of 50 to 100 mg. daily to a total of 145 to 635 mg. On the other hand, cortisone did not entirely relieve the symptoms in another case. Atropine sensitivity was relieved in two cases, and improvement is also claimed in two cases of sympathetic ophthalmia [though the details given are meagre].

[Further details of the type of asthma in these cases would be welcome; a fuller account is to be published later.] *K. Gurling.*

The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Drug Hypersensitivity Reactions. CAREY, R. A., HARVEY, A. M., HOWARD, J. E., and WAGLEY, P. F. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 354. 5 figs, 15 refs.

Five patients who were penicillin-sensitive (manifested by urticaria and angioneurotic oedema and, in two of the patients, by fever and arthritis) responded dramatically to the administration of 50 to 100 mg. daily for from 3 to 9 days of adrenocorticotrophic hormone (ACTH). Improvement was noted within a few hours and was complete in 1 to 5 days. Response was slower and less complete in another patient given 200 mg. of cortisone daily for 4 days. In four of the six patients minor relapses occurred 5 to 14 days after treatment was stopped. In one of the patients receiving ACTH there was only a minimal reaction to a further injection of penicillin.

ACTH, 100 mg. daily, was given to a patient who was sensitive to iodine (high fever, angioneurotic oedema, buccal ulceration, and exfoliative dermatitis). He responded within 48 hours, resolution being complete within 4 days. Although treatment was continued for 8 days, the condition relapsed 6 days later; it again responded to ACTH, this time permanently.

In two patients who reacted to local application of atropine to the eye (oedema of the eyelids and cornea, and dermatitis of the face) there was a rapid response to ACTH, 100 mg. daily; sensitivity to atropine was abolished, as shown by the patch test. One patient in whom there was an acute reaction to 3-hydroxy-2-phenylcinchoninic acid (HPC), given in the treatment of

chronic lupus erythematosus, received 200 mg. ACTH; resolution was rapid and there was no reaction to a further dose of HPC. An asthmatic patient who was sensitive to aspirin reacted only mildly to 130 mg. of aspirin during treatment with 140 mg. of ACTH daily and did not react to 80 mg. of aspirin after ACTH was discontinued. In two cases of hypersensitivity to sulphonamides (generalized skin eruption, stomal ulceration, and agranulocytosis) the leucocyte count returned to normal and there was some improvement in the skin condition. One of the patients, however, a man of 55, was receiving penicillin and aureomycin at the same time; the dosage of ACTH was inadequate and he subsequently died in uraemia.

Robert de Mowbray.

Skin Complications of Cortisone and ACTH Therapy. BEHRMAN, H. T., and GOODMAN, J. J. (1950). *J. Amer. med. Ass.*, **144**, 218. 7 figs, 7 refs.

The case histories of patients of the Mount Sinai Hospital, New York, are recorded in order to illustrate cutaneous complications seen there in patients under treatment with adrenocorticotrophin (ACTH) and cortisone. Three of the cases were of acute disseminated lupus erythematosus and had been treated with ACTH in doses of 90 to 100 mg. over periods of 26 to 42 days. The other patient, who had a type of recurrent erythema multiforme, had received 1·5 g. ACTH in 13 days. The skin manifestations seen were hyperpigmentation, acneiform eruptions, hirsutism, rounding of the face (moon face), striae atrophicae, delayed wound healing, and flattening of keloid scars. Cutaneous manifestations previously reported in the literature are briefly reviewed.

N. R. W. Taylor.

Observations on Changes Taking Place in the Upper Respiratory Tract of Patients Under ACTH and Cortisone Therapy. BORDLEY, J. E. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 415. 4 figs, 3 refs.

Changes have been noted in the tissues of the upper air passages under adrenal cortical stimulation by ACTH and following the administration of cortisone. During exhibition of ACTH the nasal mucous membranes lose their swelling, develop a slate-pink colour and are covered with a thin layer of clear mucus. Polyps lose their translucence, become pink and begin to shrink, in many cases disappearing completely. Such changes seem to be correlated with the initial eosinopenia developing under ACTH therapy. Changes have also been observed in the nasopharyngeal lymphoid tissue. It becomes clearly outlined from its surrounding structures, developing an orange-pink colour. Discharge around it clears up and the crypts become more prominent. Microscopic studies show no demonstrable change in such lymphoid tissue or in the nasal polyps.

The changes in the nose and nasopharynx regress after discontinuing therapy. Within a few days the nasal mucosa loses its dusky appearance, and the lymphoid tissue returns to its former state. Nasal polyps return in from 2 weeks to 2 months.

Cortisone therapy has very much the same effect on the tissue of the respiratory tract, except that no marked colour change was noted in the nasal mucosa or in the nasopharyngeal lymphoid tissue in the patients under such treatment. Nasal sprays of cortisone have resulted in a slow but definite regression of nasal polyps.—[*Author's summary.*]

Effects of Adrenocorticotropic Hormone in Pneumonia: Clinical, Bacteriological and Serological Studies. KASS, E. H., INGBAR, S. H., and FINLAND, M. (1950). *Ann. intern. Med.*, **33**, 1081. 5 figs, 10 refs.

Three patients with pneumococcal and one with viral pneumonia were treated with varying amounts of adrenocorticotrophin (ACTH); in another patient with viral pneumonia the administration of ACTH seems to have coincided with the beginning of natural recovery. These studies, made by the authors at the Boston City General Hospital, do not suggest any superiority of ACTH over the sulphonamides or penicillin in the treatment of pneumonia.

The details given suggest that full clinical control of the disease is obtained more slowly, an impression supported by the persistence of irregular fever for 8 to 12 days in two of the three pneumococcal cases and by a severe recrudescence in the 3rd, in which empyema also developed after 4 weeks, by the absence of any demonstrable effect of ACTH on the pneumococci, and by the persistence of rusty sputum or bacteriaemia despite clinical improvement. On the other hand, ACTH seems to have induced remarkable crises on the 3rd day in two patients with pneumococcal pneumonia, and a sharp lysis on the 4th day in the other. Symptomatic relief, as shown by disappearance of pain, lessening of toxaemia and headache, and general subjective improvement, was notable. The appearance of antipneumococcal antibodies and cold agglutinins was neither delayed nor accelerated. Two patients developed glycosuria and two facial oedema. There was some evidence to support an antipyretic action of ACTH. *Maxwell Telling.*

Investigations on the Urinary Excretion of Corticoids and 17-Ketosteroids during the Administration of Adrenocorticotrophic Hormone (ACTH). [In English.] SPRECHLER, M. (1950). *Acta endocrinol., Kbh.*, **5**, 101. 12 figs, 41 refs.

Adrenocorticotrophin (ACTH) was given to a series of patients of both sexes and practically all age groups who were suffering from a variety of conditions including acute and chronic rheumatism, leucoderma, scleroderma, disseminated lupus erythematosus, and Boeck's sarcoid. The ACTH was from four different batches and the dose was usually between 30 and 100 mg. daily, given in three or four divided doses. The treatment was continued for periods ranging between 4 and 125 days. Urine was collected in 24-hour lots and was assayed for 17-ketosteroids, corticoids, and occasionally glucocortoids. Ten patients showed a normal response: the urinary excretion of steroids increased on the first day of treatment and continued to increase progressively to reach a maximum on the 3rd to 5th days, then remaining fairly constantly elevated; the excretion of corticoids generally reached a maximum before that of 17-ketosteroids, and the relative increase in the excretion of corticoids was generally greater than that of 17-ketosteroids. In four other cases there was a poor response similar to that observed in Addison's disease, but none of these patients had any symptoms of Addison's disease.

A further series of five patients were given larger doses of ACTH, varying between 980 and 2,700 mg. daily,

during periods ranging between 14 and 23 days. The excretion of urinary steroids was at a high level, but after 9 or 10 days the excretion of corticoids decreased, suggesting an adequate adrenal cortical reserve. One of these patients, however, although given the high dosage, had only a very poor response throughout the period of treatment. Finally, five patients were treated for longer periods varying between 26 and 125 days. In only two was there some evidence suggesting that a refractory state developed after about 40 and 70 days respectively.

From the available data it is concluded that the minimum effective daily dose of ACTH required to produce an increased corticoid output is about 5 to 6 mg. in children and about 12 mg. in adults. The corresponding dosage required to produce an increased 17-ketosteroid output is about 12 mg. in children and 14 mg. in adults. *A. C. Crooke.*

Capillary Resistance and Adrenocortical Activity. ROBSON, H. N., and DUTHIE, J. J. R. (1950). *Brit. med. J.*, **2**, 971. 7 figs, 22 refs.

In these studies the Scarborough negative-pressure method of determining capillary resistance was used throughout. The apparatus and technique are described. The effects of heat, cold, ultraviolet radiation, *x* rays, nitrogen mustard, histamine, and T.A.B. vaccine on capillary resistance are briefly reviewed. The authors observed a rise in capillary resistance after a dose of adrenaline or insulin.

In six patients with rheumatoid arthritis, a single dose of 25 mg. adrenocorticotrophin (ACTH) caused a significant rise in resistance in 4 hours, with a delayed response in one case. With doses of 25 mg. every 8 hours capillary resistance reached a maximum in 72 hours and continued at this level until administration stopped. The resistance then fell at varying speeds, generally returning to basal levels in 10 to 14 days. The extent and speed of the rise, however, did not always coincide exactly with the percentage fall in eosinophils in the blood. In two cases of spondylitis ankylopoietica and in one out of two cases of disseminated lupus erythematosus, resistance also increased after ACTH therapy. Definite clinical remission on three occasions followed the use of ACTH in two cases of idiopathic thrombocytopenic purpura. It is suggested that the rise in capillary resistance might be due to adrenocortical stimulation by endogenous adrenaline or some similar mechanism, and that capillary resistance estimations may be used as a measure of the response of the adrenal cortex to stimulation. *N. R. W. Taylor.*

Pregnenolone. HENDERSON, E., WEINBERG, M., and WRIGHT, W. A. (1950). *J. clin. Endocrinol.*, **10**, 455. Bibl.

Pregnenolone (the 3-hydroxy derivative of progesterone) was prepared in the laboratory in 1934 and isolated from hog testis in 1943. In experimental animals it favours spermatogenesis without affecting the interstitial cells of the testis, and protects the testis against the damaging action of oestrogen. Unfortunately the effect on spermatogenesis is a maintaining and not a curative one—it prevents the loss of spermatogenes after hypophysectomy, but will not restore it once it is lost. In doses usual for steroids it has no oestrogenic, androgenic, or adrenal-cortical activity, but all these activities can be demonstrated with massive doses in particular types of experiment. It has no toxic action; mice survive single doses of 5 g. per kg. body weight without any ill effect, and very large doses can be repeatedly given during long periods without affecting their growth or fertility, or altering the blood picture.

The clinical application of pregnenolone has so far been empirical. It was first given to volunteers subjected to fatigue in experimental conditions under which the urinary 17-ketosteroid excretion is increased. This increase and other objective signs of fatigue were lessened by giving 50 mg. of pregnenolone daily by mouth. This effect has not been generally confirmed—the drug is apparently only of benefit in fatigue associated with an element of urgency or anxiety. The 17-ketosteroid excretion is increased in ankylosing spondylarthritis and can be reduced to normal by giving 50 to 150 mg. of pregnenolone daily by injection; the treatment reduces pain and muscle spasm and extends the limits of movement. In rheumatoid arthritis the 17-ketosteroid excretion is normal, but the fatigue incident to the condition suggested that the steroid might be of some benefit. Conflicting clinical reports of its effect are summarized, some of which claim relief of pain, lessening of fatigue, and in some cases measurable reduction in swelling. High dosage seems to be necessary and daily doses of 1 g. by mouth or 600 mg. by injection have been given for long periods without any side-effects being noted. Further investigation is warranted, but definite benefit has not yet been proved. The compound has no significant effect on oligospermia.

The authors point out that until a normal physiological role has been assigned to the steroid its use will remain empirical, which the remarkable absence of effects on the rest of the endocrine system makes relatively harmless. *Peter C. Williams.*

Action of Cortisone on Cardiovascular-Renal Effects of Desoxycorticosterone Acetate. FRIEDMAN, S. M., FRIEDMAN, C. L., and NAKASHIMA, M. (1950). *Amer. J. Physiol.*, **163**, 319. 1 fig., 12 refs.

The effects of cortisone acetate alone and in combination with deoxycortone (DCA) was investigated on the cardiovascular-renal system and plasma electrolyte balance of Sherman albino rats weighing 60 to 70 g. Eight animals were used in each of the control and test groups. Cortisone acetate was given in daily injections of 2·0 mg. per animal. DCA was given as subcutaneous implants weighing approximately 19 mg. Two implants were inserted on the 1st day, and one on the 4th, 8th, and 12th days of the experiment. The experiment was continued for 20 days; blood for electrolyte analysis was taken by intracardiac puncture without anaesthesia and then the animals were killed. Blood pressure was estimated by a modified tail plethysmographic method.

In all animals receiving cortisone growth was completely suppressed, an effect which was not antagonized by DCA. The blood pressure on the last 7 days of the experiment was raised in the animals receiving DCA, while cortisone appeared to inhibit the rise. The authors did not consider cortisone to be completely antagonistic to DCA as regards effects of the latter on the cardiovascular-renal system, because it failed to prevent the increase in weight of heart and kidneys produced by DCA although the blood pressure failed to rise when both

substances were given simultaneously. Moreover, the renal glomerular damage caused by cortisone was additive to that caused by DCA when both were given together. Cortisone caused an elevation of plasma potassium and chloride levels, effects antagonistic to those of DCA, but overshadowed by the latter when both were given together. Cortisone tends to cause a decrease in the number of eosinophils in the anterior pituitary; this suggests a suppression of growth hormone.

Routine histological sections were taken of kidney, heart, adrenal, spleen, pancreas, intestine, testis, and pituitary; the findings are reported. *N. R. W. Taylor.*

Effects of 17-Hydroxy-corticosterone (" Compound F ") in Man. FOURMAN, P., BARTTER, F. C., ALBRIGHT, F., DEMPSEY, E., CARROLL, E., and ALEXANDER, J. (1950). *J. clin. Invest.*, **29**, 1462. 8 figs, 18 refs.

Work with adrenocorticotrophic hormone (ACTH) has suggested that the adrenal cortex produces three types of hormone, one affecting carbohydrate metabolism (" sugar " or " S " hormone), one affecting Na and K metabolism (" Na " hormone) and one with somatotrophic and androgenic properties (" nitrogen " or " androgenic " hormone). Earlier work by the present authors indicated a possibility that " S " hormone could influence K balance and hence Na balance, so that the postulation of a separate " Na " hormone in response to ACTH stimulation is unnecessary. This paper describes the investigation on the possibility by the use of a pure " S "-hormone-like substance, 17-hydroxycorticosterone or compound F.

Compound F (50 mg.) was administered to a normal man in four doses on each of two separate days, and its effects were studied on the ensuing three days as compared with three corresponding control days, the diet being identical on all the days. The urinary excretion of nitrogen, potassium, sodium chloride, phosphorus, calcium, magnesium, and 17-ketosteroids was determined, and also the blood sugar and eosinophil levels. Glycosuria occurred after compound F on both occasions, but without a raised blood sugar level, indicating a lowered renal threshold. A fall in eosinophil count followed the injections and there was a slight loss of nitrogen, as expected. The effect on the excretion of K was more marked than on any of the other electrolytes: K loss began soon after injection, and 20 mEq. was lost before large dietary intake restored the balance. Some water and salt retention occurred, but the observations were difficult to interpret. Changes in phosphorus, calcium, and magnesium output were not significant: 17-ketosteroid excretion was slightly reduced.

The authors conclude that since compound F, with " S "-hormone-like action, reproduces the changes in K, Na, and Cl balance characteristic of ACTH, there is no need to postulate that a separate " Na " hormone is secreted when the adrenals are stimulated by ACTH.

Nancy Gough.

The *in vitro* Production of Cortisone by Mammalian Cells. SENECA, H., ELLENBOGEN, E., HENDERSON, E., COLLINS, A., and ROCKENBACH, J. (1950). *Science*, **112**, 524. 6 refs.

Adrenal tissue was incubated at 37° C. in a complex nutrient medium with deoxycortone, and the formation of corticosterone determined by extraction and examination by paper chromatography. The addition of vitamins C, B_1, B_2, and B_6, nicotinic acid, and insulin gave the best results, omission of any or all of these materials giving lower yields of cortisone. Addition of glutathione to this optimum medium gave completely negative results. The highest positive results were given by the adrenals of the cat and man (one case) followed by the dog, rat, and guinea-pig, those of the chicken being negative. Liver, testis, kidney, and ovary gave a few positive results. *F. W. Chattaway.*

The Excretion of Urinary Neutral 17-Ketosteroids following Bilateral Splanchnicectomy and Right Adrenalectomy. MICHIE, E. A., and CLAYTON, B. E. (1950). *J. Endocrinol.*, **6**, 423. 1 fig., 13 refs.

An investigation into the urinary excretion of neutral 17-ketosteroids was carried out in the Clinical Endocrinology Research Unit (M.R.C.) at the University of Edinburgh, on two women, aged 48 and 39 respectively, before and after undergoing sympathectomy for hypertension. Bilateral splanchnicectomy was performed in both cases, the greater splanchnic nerve being divided, the sympathetic chain removed from T8 to L3, and all communications to the coeliac ganglion from the spinal nerves divided just short of the ganglion. In one patient the right adrenal gland was also removed. The operation was performed in two stages with an interval of more than 10 days; repeated estimations were made of 17-ketosteroids excretion over a control period before operation (15 weeks in one case and 2 weeks in the other), during the interval between the two stages of the operation, and for 4 to 8 weeks subsequently. Fluctuations in 17-ketosteroid excretion which usually occur after operation or trauma were thus allowed for.

Forbes and others (*J. clin. Endocrinol.*, 1947, 7, 264) observed an initial rise in 17-ketosteroid excretion after various forms of trauma, followed by a fall and return to normal within 10 days, but this was not found in the two cases reported here. Although there was considerable day-to-day fluctuation in 17-ketosteroid excretion (mainly between 4 and 12 mg. daily in one patient and between 3 and 6 mg. daily in the other), the operation had no significant over-all effect on the level of excretion. Since the operations involved complete division of the nerve-supply to the adrenals in both cases, and in one case the removal of one adrenal as well, it would appear that the excretion of 17-ketosteroids is not under nervous control, and that when one adrenal is removed the other can compensate for it adequately. *Robert de Mowbray.*

The Effects of Adrenaline on the Number of Circulating Eosinophils and on the Excretion of Uric Acid and Creatinine. [In English.] BROCH, O. J., and HAUGEN, H. N. (1950). *Acta endocrinol., Kbh.*, **5**, 143. 8 refs.

From the results obtained in a series of 23 control subjects and six patients with Addison's disease who were given subcutaneous injections of 0·3 to 0·5 mg. adrenaline, it was concluded that the changes in the number of circulating eosinophil cells and in the concentration of uric acid 4 hours afterwards were too variable to serve as a useful clinical test of adrenal cortical function. *A. C. Crooke.*

Effect of Cortisone and ACTH on Eosinophils and Anaphylactic Shock in Guinea-Pigs. DWORETZKY, M., CODE, C. F., and HIGGINS, G. M. (1950). *Proc.-Soc. exp. Biol., N.Y.*, **75**, 201. 4 figs, 12 refs.

Guinea-pigs were used throughout this study. The number of eosinophils in the blood of males was significantly lower than that in females. Cortisone reduced the number of eosinophils in the blood of males and females. ACTH produced a pronounced eosinopenia in males and nonpregnant females. Pregnancy abolished the eosinopenic effect of ACTH. Neither cortisone nor ACTH had any effect upon the degree of anaphylactic shock produced in guinea-pigs by the intravenous injection of the agent to which the animals had been sensitized.—[*Authors' summary.*]

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The Treatment of Chronic Joint Disorders with Adrenal Cortical Extract. (Zur Behandlung chronischer Gelenkleiden mit Nebennierenrindenwirkstoffen.) KÖHLBRANDT, K., MEYER, W., and ROESENER, G. (1950). *Neue Med. Welt.*, **1**, 1450. 38 refs.

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